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INTRODUCTORY STATEMENT

THE editors of the JOURNAL OF CHRONIC DISEASES are pleased to announce the start of what we hope will prove to be a popular and useful regular feature of the JOURNAL. Dr. Victor McKusick and his colleagues have prepared an annotated review of medical genetics for 1958. It is their plan to produce annually what might be called an "annual review of medical genetics," a small "yearbook of medical genetics," or "recent advances in medical genetics." It is intended that the publications in each calendar year will be surveyed and that the resulting review will be published as early as possible in the year that follows, if possible in the first six months. It is hoped that the accumulation of annual reviews will prove a substitute for a full textbook of medical genetics—which many feel is badly needed but few have the time to undertake—and will supplement the available textbooks in the field of general genetics and human genetics.

Reprints for use in connection with future reviews are solicited. They should be addressed to *Dr. Victor A. McKusick, The Johns Hopkins Hospital, Baltimore 5, Maryland.* Individual copies of this issue will be available from the publisher for the usual price of $2.

The Editors

It is a pleasure to acknowledge the assistance of the following persons who were members of our group during part or all of 1958: R. M. Bannerman, N. O. Borhani, S. H. Boyer IV, A. W. Chisholm, B. H. Cohen, A. E. Dormer, D. A. Price Evans, J. A. T. Hancock, J. T. Leeming, A. M. Lilienfeld, A. B. McKusick, K. A. Manley, C. F. Merryman, E. A. Murphy, J. H. Renwick, J. T. Scott, A. P. Skyring, Soon Kyu Suh, W. J. Young, and M. Zomeña.

MEDICAL GENETICS
1958

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INTRODUCTION

THE operation of genetic factors is observable in all areas of medicine. Therefore, it is necessary to be eclectic in the preparation of a review of medical genetics. This review will concern itself with the following aspects:

1. Analysis of phenotypic features which may have a bearing on recognition of heterogeneity of given "entities," on the mechanism of gene action, on the early detection of the disease or the presence of the gene, and so on.

2. Information, especially biochemical, bearing on the "basic defect" and the mechanism of gene action, the chain leading from gene to disease.

3. The formal genetics—mode of transmission, dynamics in populations, linkage, etc. Evidence of the familial aggregation of diseases which are probably the result of multiple genetic and environmental factors will be included.

4. For the most part, preventive and therapeutic measures will be mentioned only when they are judged to have a bearing on the more strictly genetic aspects of the disease, are based on present understanding of the mechanism of the disease, or shed light on that mechanism.

The review will attempt a critical appraisal of reports and will try to avoid becoming a simple "cumulative index." It is recognized as an unavoidable possibility that some significant contributions will be missed. Every attempt will be made, however, to avoid major omissions.

The review will be organized in sections as indicated below. (In the case of many topics which could legitimately be discussed with any one of several systems, arbitrary assignment to position in the review will be necessary.)

1. New books, journals, symposia, congresses
2. History
3. General genetics (selected reports)

4. Human genetics, general considerations
5. Methods: statistical, biochemical, and others
6. Biochemical genetics
7. Congenital malformations
8. Alimentary tract, including salivary glands, pancreas, and liver
9. Blood and hematopoietic system
10. Cardiovascular system
11. Connective tissue
12. Ear
13. Endocrine system
14. Eye
15. Genital system
16. Muscle
17. Neoplasms
18. Nervous system, including psychiatric disorders and mental defect
19. Skeleton
20. Skin and its accessories
21. Teeth
22. Urinary system
23. Miscellaneous

References include full titles. Each paragraph is numbered to permit cross references in this review and in future reviews.

It is anticipated that these reviews will be particularly useful to two groups: to clinicians who find it difficult to keep up with genetic aspects in their own specialty as well as in others, and to general geneticists and human geneticists who do not have ready access to the clinical literature.

I. NEW BOOKS, JOURNALS, SYMPOSIA, CONGRESSES

A. New books.—

1. Allen, F. H., Jr., and Diamond, L. K.: Erythroblastosis Fetalis, Including Exchange Transfusion Technic, Boston, 1958, Little, Brown and Company.

Most of the material of this small book originally appeared as a "Medical Progress" article in the *New England Journal of Medicine* in October, 1957. The section on exchange transfusion has been added. The result is a highly useful and interesting survey of the problem.

2. Alvarez, W. C.: Practical Leads to Puzzling Diagnoses: Neuroses That Run in Families, Philadelphia, 1958, J. B. Lippincott Company.

This book is included to condemn it. The theme of the book is that mental instability manifested by psychosis, alcoholism, epilepsy, constitutional inadequacy, hypochondriasis, unemployability, neurocirculatory asthenia, and so on, is hereditary and that by recognizing this fact and looking into the family history many otherwise puzzling "cases" can be unraveled. However true may

be the premise, the manner in which it is presented and dragged out for almost 500 pages—and the complete lack of controls—forces one to agree with the *J.A.M.A.* reviewer that "the book is medical fiction." The author has done a disservice to medical genetics. The lack of both psychiatric and genetic understanding is evident throughout.

3. Barsky, A. J.: Congenital Anomalies of the Hand and their Surgical treatment, Springfield, Ill., 1958, Charles C Thomas.

Although this is not primarily a genetic treatise and no worth-while contribution to this aspect is made, a brief chapter is devoted to the genetic factor in these anomalies. The book is useful only in demonstrating some of the variety of malformations of the hand which can occur.

4. Bean, W. B.: Vascular Spiders and Related Lesions of the Skin, Springfield, Ill., 1958, Charles C Thomas.

Much of genetic interest is to be found in this book by a master clinician who through many years of painstaking observation has accumulated an enviable experience. The genetic disorders discussed include hereditary hemorrhagic telangiectasia, Sturge-Weber syndrome, angiokeratoma corporis diffusum universale of Fabry, pseudoxanthoma elasticum, the nape nevus, Peutz-Jeghers' mucocutaneous melanin pigmentation and intestinal polyposis, and tuberous sclerosis.

5. Darwin, Charles: Autobiography. Edited, with original omissions restored, by his granddaughter Nora Barlow, London, 1958, William Collins Sons & Co., Ltd.

This is a full publication written in beautiful English and giving the autobiographer's candid views of persons and practices. Other material interesting to medical geneticists, such as a bibliography on Darwin's health and the Darwin family tree, is included.

6. de Grouchy, J.: L'hérédité moléculaire. Conditions normales et pathologiques, Rome, 1958, Gregor Mendel Institute (No. 7 of Analecta Genetica, edited by L. Gedda).

The author, a young member of Professor Lamy's group at the Hôpital des Enfants-Malades in Paris, studied for a time in Neel's department at Ann Arbor. His book, in French, is divided into two parts. The first discusses bacterial transformation, transduction in bacteriophage, DNA structure, duplication of DNA, DNA and RNA in protein synthesis, the gene as a unit of function, mutation and crossing over, pseudoallelism, genes and enzymes, genes and nonenzymatic proteins, etc. The second part discusses pathologic states which in recent years have been increasingly understood, some at the biochemical level: phenylketonuria, galactosemia, glycogen storage diseases, Wilson's disease, heritable disorders of connective tissue, von Recklinghausen's neurofibromatosis, intestinal polyposis, Rh factor, disorders of clotting, hemoglobinopathies. Each discussion is authoritative from both the clinical and the genetic point of view. Full refer-

ences to the literature are provided. The author is much to be congratulated on the final product. Since he confines himself to those conditions on which the information is sound and relatively ample he has reviewed the status of medical genetics in an admirable manner.

7. Garn, S. M., and Shamir, Z.: Methods for Research in Human Growth, Springfield, Ill., 1958, Charles C Thomas.

Complete details for the pursuit of growth studies, even the architectural layout of Dr. Garn's department at the Fels Research Institute in Yellow Springs, Ohio, are given. Longitudinal and cross-sectional methods are compared. X-ray techniques for various measurements and determination of bone age are covered. (The authors present a family in which 6 of 7 siblings showed an anomalous pattern of carpal ossification: whereas the greater and lesser multangular and navicular bones ordinarily begin to calcify 2 to 3 years before the ulnar epiphysis, exactly the reverse occurred in this family and is observed fairly often in other families.) Development of the teeth, skin (e.g., changes in pigmentation with aging), hair, fat, breasts, etc., is discussed, as well as statistical and graphical methods.

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8. Hutt, F. B.: Genetic Resistance to Disease in Domestic Animals, Ithaca, 1958, Cornell University Press.

Essentially Professor Hutt of Cornell University has provided a survey of veterinary medical genetics. It is of great interest to medical genetics to compare the problems in the two fields and to observe the operation of many of the same principles: identification of heterozygous carriers of a recessive disease trait, genetic variations in susceptibility to infectious disease and study of the mechanism of these gene-determined variations, balanced polymorphism, pseudopleiotropy as the basis of syndromes, biochemical genetics in animals, and so on. See Bull. Johns Hopkins Hosp. 103:151, 1958, for long review.

9. Kalmus, H.: Variation and Heredity, London, 1958 (planned for 1957), Routledge & Kegan Paul, Ltd.

This is a readable, accurate, and useful semipopular treatment of human heredity and its bearing on society.

10. Lamy, M.: L'hérédité; éléments fondamentaux de génétique. Horizons médicaux, No. 45-54. Paris, 1957-1958, Laboratoire de l'Hepatrol.

After presenting some basic principles of genetics in man, Lamy reviews medical genetics with particular reference to conditions about which sound information is available.

11. McCullagh, D., and Swanker, W. A.: Anomalies of Infants and Children, New York, 1958, McGraw-Hill Book Company, Inc.

The promising title proves a disappointment. The authors, surgeons, have included burns and injuries in their book, demonstrate bizarre concepts of causation, and make many statements which are undoubtedly wrong, even dangerous.

No balanced or adequate coverage is provided; more space is given to blepharoptosis than to cardiac malformations.

12. McElroy, W. D., and Glass, B., editors: The Chemical Basis of Development, Baltimore, 1958, The Johns Hopkins Press.

The McCollum-Pratt symposium on development held in March, 1958, was a logical sequel to the symposium on the Chemical Basis of Heredity held in 1956. All parts of the new symposium have genetic pertinence. The role of the nucleus in development (Mirsky and Allfrey), chromosomal differentiation (Gall), and the role of genes in the developmental processes (Hadorn) are discussed among many other aspects, in this detailed treatment of the current state of knowledge in the field of embryology.

13. Mourant, A. E., Kopeć, A. C., and Domaniewska-Sobczak, K.: The ABO Blood Groups; Comprehensive Maps and Tables of World Distribution, Springfield, Ill., 1958, Charles C Thomas.

The authors have performed the Herculean task of culling the vast literature, classifying the data on the distribution of ABO groups and A subgroups, computing gene frequencies, and assembling all the information in a single volume. It is an important contribution to physical anthropology and to investigation in the relationship of blood groups and disease.

14. Pontecorvo, G.: Trends in Genetic Analysis, New York, 1958, Columbia University Press.

This is an amplified form of lectures delivered at Columbia University in 1956. The monograph is a superb statement of present knowledge of the nature of the gene.

15. Race, R. R., and Sanger, R.: Blood Groups in Man, ed. 3, Oxford, 1958, Blackwell Scientific Publications.

The inheritance of the blood groups is discussed in admirable detail and clarity. Blood groups in twins, in disputed parentage, in disease (hemolytic disease of the newborn; susceptibility to disease), and linkage studies are discussed. A useful list of inherited characters for which linkage with blood group loci has been sought is provided; about 44 separate characters are listed. Interracial transfusions are mentioned as a possible way in which new blood group antigens will be discovered.

It is useful to historic perspective to note the dates of discovery of the several blood groups systems:

ABO blood groups	1900 (Landsteiner)
A_1A_2 subdivisions	1911 (van Dungern and Hirszfeld)
MN blood groups	1927 (Landsteiner and Levine)
MNSs subdivisions	1947 (Walsh and Montgomery)
P blood groups	1927 (Landsteiner and Levine)
P_1P_2 subdivisions	1955 (Sanger)

Salivary secretion of ABO antigen	1930 (Lehrs and Putkonen)
Rh blood groups	1937 (Landsteiner and Weiner)
Lutheran blood groups	1946 (Callender and Race)
Kell blood groups	1946 (Coombs, Mourant, and Race)
Lewis blood groups	1946 (Mourant)
Lewis saliva groups	1949 (Brendemoen; Grubb)
Duffy blood groups	1950 (Cutbush, Mollison and Parker)
Kidd blood groups	1951 (Allen, Diamond, Niedziela)
Diego factor	1954 (Levine and associates)

16. Sinott, E. W., Dunn, L. C., and Dobzhansky, T.: Principles of Genetics, ed. 5, New York, 1958, McGraw-Hill Book Company, Inc.

This and Srb and Owen's *General Genetics* (W. H. Freeman & Company, 1955) are the standard textbooks of general genetics and are those we have used in the general genetics portion of our medical genetics curriculum.

17. Thannhauser, S. J.: Lipidoses, Diseases of the Intracellular Lipid Metabolism, ed. 3, New York and London, 1958, Grune & Stratton.

This is a useful source book for information on some limited aspects of hereditary disorders of fat metabolism, such as familial hyperlipemia, familial hypercholesterolemia, Niemann-Pick's disease, and Gaucher's disease. Genetic aspects are weak. The book is riddled with typographical errors—two on the same line in the Preface—which apparently involve mainly the parts added in this new edition. The Hurler syndrome is still included. Although at the end of the chapter it is stated that the Hurler syndrome is not a lipidosis, the first part of the chapter has not been rewritten and conveys the impression that it is a lipidosis. Although this compendium will have some usefulness, most readers will not find its usefulness commensurate with its staggering price.

18. Watson, E. H., and Lowrey, G. H.: Growth and Development of Children, ed. 3, Chicago, 1958, The Year Book Publishers, Inc. A good treatment of the subject is provided.

19. Wiener, A. S., and Wexler, I. B.: Heredity of the Blood Groups, New York, 1958, Grune & Stratton.

This smallish book covers essentially the same ground as does that of Race and Sanger. It is a condensed version of Wiener's early books (*Blood Groups and Transfusion*, 1943; *Rh-Hr Blood Types*, 1954; *Rh-Hr Syllabus*, 1954) brought up to date, with special emphasis on genetics.

20. Winchester, A. M.: Genetics, a Survey of the Principles of Heredity, ed. 2, Boston, 1958, Houghton Mifflin Company.

This is a readable exposition. Presumably for the purpose of heightening interest in genetics on the part of university students, many examples are drawn from man. The presentation, as in many textbooks designed for college use, is

open to the serious criticism that the inheritance of many morphologic traits such as ear-lobe type, is discussed in a manner to suggest that the inheritance is simpler than it truly is and that these traits would be useful, for example, in linkage studies. Most of these traits have not been exposed to the systematic genetic study they may deserve. Some disease traits are covered by Winchester but the book is, of course, not a treatise on medical genetics. There are some inaccuracies, and oversimplification may lead to failure to stimulate the interest and curiosity of capable students.

B. Journals.—

21. The following periodical journals are devoted, partly or exclusively, to human and medical genetics:

Acta geneticae medicae et gemellologiae (Rome)	Vol. 7
Acta genetica et statistica medica (Basel)	Vol. 8
American Journal of Human Genetics (Baltimore)	Vol. 10
Annals of Human Genetics (formerly Annals of Eugenics) (London)	Vols. 22-23
Eugenics Quarterly (New York)	Vol. 5
Eugenics Review (London)	Vol. 50
Folia hereditaria et pathologica (Milan)	Vol. 7
Japanese Journal of Human Genetics	Vol. 3
Journal de génétique humaine (Geneva)	Vol. 7

22. The following journals also contain material on human genetics:

American Journal of Physical Anthropology (Philadelphia)	Vol. 16
Genetica (The Hague)	Vol. 29
Genetics	Vol. 43
Hereditas	Vol. 45
Human Biology (Detroit)	Vol. 30
Journal of Genetics	Vol. 56
Journal of Heredity (Washington)	Vol. 49

C. Symposia.—

23. The American Heart Association, at its annual meeting in San Francisco in October, sponsored a half-day symposium on genetic factors in diseases of the cardiovascular system. The discussion was divided into five parts: atherosclerosis including coronary artery disease; hypertension; susceptibility to rheumatic fever; congenital malformations of the cardiovascular system; and cardiovascular involvement in syndromes due to pleiotropic genes.

April 7-10, 1958, the new Department of Medical Genetics in the Medical School at the University of Wisconsin, Madison, was inaugurated with an international symposium covering current research in human genetics. Participants included Koprowski, Stocker, Atwood, Stern, Pontecorvo, Ceppelini,

Owen, Neel, Graham, Steinberg, Boyd, Glass, Levine, and Matsunaga. The symposium will be published in the *Journal of Medical Education* and in the *American Journal of Human Genetics.*

The American College of Physicians in April (Alving; McKusick; Neel) and the New York Academy of Medicine in October (Childs; Janeway; McKusick) sponsored symposia on genetics and disease.

The New York Academy of Sciences sponsored a symposium on "Genetic Concept for the Origin of Cancer" (Strong). Strong provided a historical review. Bittner, Heston, Gowen, Gordon, and others discussed the genetics of cancer in lower forms. Failla discussed aging and carcinogenesis. Sinnott and Dobzhansky contributed. Gorer and Oliver surveyed methods for studying the genetics of cancer in man.

The American Society of Hematology, meeting at Atlantic City on April 26, 1958, devoted half a day to papers on thalassemia: its nature and definition (Zuelzer), geographic distribution (Chernoff), the abnormality of heme syntheses (Bannerman, Grinstein, Moore), electrophoretic investigations of hemoglobin (Diamond and Gerald; Kunkel; Ceppelini and Dunn) and splenectomy (Carl Smith).

D. Congresses.—

Tenth International Congress of Genetics, Montreal, Aug. 20-27, 1958—Selected Reports. Abstracts of the papers referred to are found in the voluminous published proceedings of the Congress. Critical evaluation must await publication of the full reports. Mention here may serve the useful function of indicating current work.

24. McLaren and Michie (London) analyzed the influence of uterine environment on the expression of genes controlling the number of lumbar vertebrae in the mouse. Reciprocal crosses indicate that deficiency in lumbar vertebrae is a "matroclinous trait." Kalter (Cincinnati) analyzed the interplay of genotype and environment in the congenital malformations produced by maternal riboflavin deficiency (produced with the antimetabolite galactoflavin) in mice. Trasler and Fraser (Montreal) provide a similar analysis for cortisone-induced cleft palate in mice.

Bernstein and Stevens (Bar Harbor) described an autosomal recessive lethal in mice manifested by jaundice and severe microcytic anemia. In mice homozygous for genes W, W^v, and W^j, which ordinarily show severe macrocytic anemia and die soon after birth, Elizabeth S. Russell and colleagues (Bar Harbor) could restore hematologic normality by transplantation of hematopoietic liver cells from histocompatible embryos.

25. Beatty (Edinburgh) has been seeking variations in spermatozoa which may represent a somatic character of the uniploid genotype and also bimodality in the characteristics of the sperm of a single individual which may indicate segregation for a single locus.

26. Sutton (Ann Arbor) found that the gene frequency for Hp^1 (haptoglobin 1) varies from 0.80* in Negroes to 0.18 in Asiastic Indians.

By starch gel electrophoresis Smithies (Toronto) found a new beta globulin called D (C = "normal") in 2 of 49 New York Negroes and 5 of 23 Australian aborigines, but in no Canadians.

The genetics of the normal EEG (Vogel, Berlin), handedness (Falek), and the Gm (for gamma) serum protein groups (Lawler, London) was reported on.

27. Gartler (Seattle) thinks genetic variations in urinary excretion of beta-aminoisobutyric acid are not determined by variations in renal function but rather by variations in thymine metabolism. Tashian (Ann Arbor) found a genetic variability in capacity for an enzyme adaptation: in some individuals repeated administration of D-phenylalanine resulted in progressively greater excretion of D-phenylpyruvic acid.

28. Kalmus (London) showed a movie which demonstrated how the world looks to the color-blind. The American Navy, in making the film, had the assistance of one of the rare persons with unilateral color-blindness.

29. Tonaka and Ohkura (Tokyo) found the following reproductive histories, in comparing x-ray technicians with pharmacists:

	MALE X-RAY TECHNICIANS	MALE PHARMACISTS
	N = 232	N = 300
Sterility	13.8%	6.0%
Stillbirth, abortion in offspring	6.31	3.54
Sex ratio of offspring	55.25	52.59
Exposure	>35 r/yr.	

30. A 20-year-old girl with bilateral asymmetry in hair and eye pigmentation was described by Ahuja (Berkeley) who postulated some mechanism such as somatic mutation, somatic deletion, or abnormal distribution of chromosomes in development.

31. Motulsky (Seattle) reported a valuable historical "find": *Hereditary Properties of Diseases, Based on Clinical Observation*, published by Joseph Adams (1756-1818) in 1814 in London. In it Adams (1) distinguished between congenital, familial ("recessive"), and hereditary ("dominant"); (2) indicated the role of consanguinity in recessive disease; (3) pointed out that the manifestation of a genetic disease might not be present at birth and might have its onset at any age; (4) emphasized that environmental factors may be necessary for the expression of genetic susceptibility, etc., etc.

32. Harvald and Hauge (Copenhagen) described what they term a catamnestic (from diagnosis to death) study of twins born from 1870 to 1910 in Den-

*The usual convention for stating gene frequencies is followed here. For example 0.80 means 80 per cent.

mark. They find a significantly higher concordance rate in monozygotic twins than in dizygotic twins for bronchial asthma, diabetes, gallstone, goiter, migraine, schizophrenia, manic-depressive psychosis, and mental deficiency. No difference in concordance rate for various forms of malignant growth and of arteriosclerotic heart disease could be demonstrated.

33. Koch (Münster, Germany) suggested that most microcephaly is due to a single factor inheritance as an autosomal recessive. Haberlandt (Münster) found in Westphalia, Germany, 251 cases of amyotrophic lateral sclerosis in a 20-year period. In 13.5 per cent there was a family history of others affected. He thinks the disease may be an autosomal dominant with incomplete penetrance and varying expressivity.

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34. Brage (Buenos Aires) found aminoaciduria without cupruria in some normal relatives of patients with Wilson's disease. He thinks these individuals are heterozygotes and that the aminoaciduria must be a primary defect in Wilson's disease and not secondary to the disturbance in copper metabolism.

35. In hypophosphatasia, an osteodystrophy in which there is large excretion of ethanolamine phosphate, Harris and Robson (London) found some excretion of the same material in about 60 per cent of persons expected to be heterozygotes. Because of intrafamilial similarities in clinical behavior of cases and in the ease of heterozygote identification, they suggested that different genes may be responsible for the same clinical picture.

36. Lewis and Li (Pittsburgh) presented the following interesting data on 116 hemophilia families:

	DEFECT	MULTIPLE SIBSHIPS OR GENERATIONS INVOLVED
Hemophilia A	Deficiency of antihemophilic globulin	43%
Hemophilia B	Deficiency of plasma thromboplastin component	52%

	TOTAL OFFSPRING	MALES		AFFECTED MALES		
		NUMBER	PER CENT	NUMBER	PER CENT OF TOTAL MALES	EXPECTED
	Offspring of Daughters of Hemophiliacs					
Hemophilia A families	159	79	49.7	41	52	50%
Hemophilia B families	74	49	66.0	22	41	50%
	Offspring of Sisters of Hemophiliacs					
Hemophilia A families	452	233	51.5	77	33	25%
Hemophilia B families	76	37	48.7	12	30	25%

They commented on the high segregation for males in the offspring of daughters of hemophiliacs and possibly for hemophilia in the male offspring of sisters

of hemophiliacs. Either could be a source for a supply of hemophilia genes to compensate in part for those lost through selection.

37. Siniscalco, Bianco, Montalenti, and Silvestroni (Rome, Naples) think there may be a direct effect of the thalassemia gene on physical measurements, a pleiotropic effect.

38. Uchida (Toronto) concluded that hypercholesterolemia is an autosomal dominant. A hypercholesterolemic child appeared to be a homozygote. Hypercholesterolemia was present in the families of both parents. Hirschhorn and Wilkinson (New York) came to a comparable conclusion. They also suggested multiple allelism as an explanation for conflicting views on the inheritance of hypercholesterolemia. It is not clear what evidence there is for this hypothesis.

39. In a large North Carolina kindred in which about 3,000 individuals were investigated, Whittinghill and his associates (Chapel Hill) found the following familial aggregation for rheumatoid arthritis and for ankylosing spondylitis among the relatives of probands with one or the other of these two disorders:

	RELATIVES AFFECTED BY SAME DISEASE		
PROBAND	1ST DEGREE*	2ND DEGREE	3RD DEGREE
Rheumatoid arthritis	3.7±1.14%	2.4±0.64%	2.3±0.60%
Ankylosing spondylitis	6.3±2.48%†	2.9±1.16%	0.7±0.5%†

The following table indicates the convention with regard to degree of relationship:

DEGREE OF RELATIONSHIP	RELATIVE	NUMBER OF STEPS IN RELATIONSHIP	DEGREE OF HEREDITARY LIKENESS, I.E., PROBABILITY THAT RELATIVE CARRIES SAME GENE
First degree	Sib, parent, child	1	1/2
Second degree	Half-sib, uncle, aunt, nephew, niece, grandparent, grandchild	2	1/4
Third degree	1st cousin, great aunt or uncle, great grandparent, great grandchild	3	1/8
Fourth degree	1st cousin, once removed	4	1/16
Fifth degree	2nd cousin	5	1/32
General case	——	n	$1/2^n$

(From Table XXIII of Penrose's *The Biology of Mental Defect*, London, 1954, Sedgewick & Jackson.)

The Oxford Dictionary gives the following definitions for degrees of relationship. It will be noted from comparison with the table that the canonical definition is the genetically accurate one. "In the Civil Law the degree of relationship between collaterals is counted by the number of steps up from one of

*First degree relatives: parents, sibs, children. Second degree relatives: grandparents, aunts and uncles, grandchildren, etc.

†Includes cases of Still's disease.

them to the common ancestor and thence down to the other; according to the canon law by the number of steps from the common ancestor to the party more remote from him; uncle and niece are according to the former related in the third, according to the latter in the second degree."

40. Hughes and Syrop (Richmond, Virginia) described absence of the orifice of Stensen's duct in 9 persons in 3 generations of one family. The mouth was dry and severe caries occurred. The parotid could not be felt. In 2 the lacrimal glands were absent or displayed disturbed function. The trait seems to be an autosomal dominant.

41. Bennett and Robson (Adelaide) suggested on the basis of family studies—which they admit are difficult—that kuru is a genetic disorder. It is responsible for about 60 per cent of the deaths of females and 10 per cent of the deaths of males in the New Guinea tribe studied.

42. Kloepfer (New Orleans) has been studying a syndrome which has probably not been previously described: 22 members of 4 sibships which are descendant from a common ancestor appeared normal until 1 to 2 months of age, then showed severe blistering in sunlight. The erythema tended to subside by the age of 5 or 6 years. Weight and height did not increase further after this time. Mental age never exceeded the imbecile level. There was progressive dementia and loss of vision. Death occurred between 20 and 31 years of age. The condition is an autosomal recessive.

43. Stiles (East Lansing, Michigan) reported on Mongoloid idiocy in mother and child.

44. T. E. Reed (Ann Arbor) pointed out that in Huntington's chorea relative fitness in terms of mean number of children is "normal" for choreic persons when comparison is made with normal sibs but low if made with the general population.

45. Blumel and co-workers of Galveston obtained information on 50 cases of anomaly of the sacrum and coccyx by sending questionnaires to orthopedists in many parts of the world. In 30 of the 50 there was complete absence of the coccyx and sacrum. In 8 there was a family history of congenital anomalies. Freire-Maia and colleagues from Brazil have reinvestigated the interesting family with achiropody (absent hands and feet) which is pictured in many textbooks of genetics. It is the only one reported. They were able to find 6 other such families. On the basis of their restudy they think the trait is autosomal recessive, not dominant as earlier thought.

46. The *major addresses* of the Congress, over 30 in number, were published in full in Volume I of the Proceedings of the Congress (which appeared in 1959). The following are a few of these:

Genetic aspects of schizophrenic psychoses. Jan A. Böök (Uppsala).
Etudes sur l'étiologie de la gémellité chez l'homme. Maurice Lamy and Jean Frézal (Paris).
Some recent developments in human biochemical genetics. H. Harris (London).
Aspects of the genetic control of the structure of the hemoglobin molecule. James V. Neel (Ann Arbor).
Some further observations on associations between blood groups and disease. J. A. Fraser Roberts (London).
Problems of comparative genetics in mammals. H. Nachtsheim (Berlin).
Immunogenetics. Ray D. Owen (Oak Ridge).
Some data on the genetic structure of human populations. L. L. Cavalli-Sjorza (Parma).
Genetics and the destiny of man. Theodosius Dobzhansky (New York).
Genetics, the gene, and the hierarchy of biological sciences. Sewall Wright (Madison).
Panel on the teaching of genetics. Bentley Glass (Baltimore), moderator.

It is impossible to review these addresses. However, a few points of particular interest are mentioned in the paragraphs which follow.

47. Böök reviewed the epidemiology, genetic hypothesis, mode of inheritance, and biochemistry of schizophrenia. He suggested that the biochemical study of a monozygotic twin pair in which only one twin had manifested schizophrenia might be helpful in distinguishing cause and effect.

48. Lamy and Frézal concluded that both environmental and genetic factors are demonstrably involved in dizygotic twinning but that the factors determining monozygotic twinning are obscure. They pointed out the amazing uniformity in the rate of monozygotic twinning throughout the human species. Factors influencing the rate of dizygotic twinning, including maternal age and birth rank, were discussed.

49. Harris, in reviewing human biochemical genetics, pointed out that "one not unfruitful approach . . . has been the routine and rather blind search for unusual metabolites in the body fluids and urine of patients with diverse inherited syndromes in the hope of uncovering metabolic disturbances . . . ." Harris' newly discovered cystathioninuria is a case in point: A mentally defective child excreted about 500 mg. a day of cystathionine, an intermediate in the formation of cysteine from methionine. Normally none is excreted. Increased amounts were also found in the tissues at autopsy and, in lower concentrations, in the urine of two ostensibly normal close relatives of the proband.

Harris raised the likelihood that renal transport defects, e.g., cystinuria, may be models for systems and defects in systems elsewhere in the body. Transport systems may be involved in maintaining concentration gradients across cell membranes. Defects in such systems might simulate an enzyme defect of intermediary metabolism.

Harris pointed out that Gitlin, Hitzig, and Janeway (1956) demonstrated in agammaglobulinemia that there is a defect not only in formation of gammaglobulins but also of at least two electrophoretically and immunologically distinct beta-globulins.

In addition to idiopathic ahaptoglobinemia an exception to the generally confirmed Smithies-Walker (1956) scheme for inheritance of haptoglobins is represented by the demonstration of Siniscalco and others that in three interrelated families five 2.2 children were derived from families in which one parent was 1.1. In each case the mother was the exceptional parent, making illegitimacy very unlikely.

50. Neel presented a useful table listing the abnormal hemoglobins together with the names of the discoverers and the year of discovery. He discussed in considerable detail the formal genetics, the biochemical genetics, and the population genetics of these disorders, as well as thalassemia.

51. Nachtsheim presented a table listing 40 hereditary diseases which occur in man and in one or more other mammals. He discussed the production of the same clinical picture, or phenotype, by different nonallelic genes, and referred to these "mimic genes" as "genocopies." The term "phenocopy" as introduced by Goldschmidt refers to an environmentally induced disorder simulating a genetic disorder. Genocopy seems a useful term for the situation such as elliptocytosis in which the seemingly identical disease can be produced by genes, which appear from the linkage data to be distinct. It was pointed out that, just as many different forms of hemophilia have been demonstrated in man, in mice more than a dozen genocopies of choreiform motion disturbances, or "dancing mice," have been described. A pedigree of causes showing the basis of apparent pleiotropy of the "crinkled" gene in the mouse was shown. Comparative genetics, especially in mammals, is useful in radiation genetics. The demonstration that the mouse is about fifteen times more sensitive to the genetic effects of radiation helped silence the objections of earlier years that "Man is no fly."

52. Cavalli-Sforza discussed the genetic structure of human populations, basing his remarks on his studies of the Parma Diocese in northern Italy. The geography varies from sparsely populated mountains to densely populated plains. The economy is mainly agricultural. Clustering, migration, consanguinity, and blood group gene frequencies were considered.

53. The *exhibits* were especially memorable. For example, the Roscoe B. Jackson Memorial Laboratory exhibited a "live linkage map of the mouse." Of more than 200 mutants, about 100 have been assigned to one of 16 linkage groups corresponding to 16 different chromosome pairs. Four chromosome pairs remain "unmarked." The linkage relationships, together with live mice showing the trait, were demonstrated.

E. Other Events and Items of Note.—

54. The Nobel Prize in Medicine and Physiology was awarded to Joshua Lederberg of the University of Wisconsin for his work in bacterial genetics and to George W. Beadle (California Institute of Technology) and Edward L. Tatum

(Rockefeller Institute) for their work in biochemical genetics using *Neurospora crassa*. Lederberg demonstrated sexual recombination in bacteria, transduction by phage (opening new possibilities of relationships between genes and viruses), and the linear arrangement of the genetic material in bacteria. Part of this work was done in collaboration with Tatum. The work of Beadle and Tatum led to the "one-gene-one-enzyme" hypothesis which has been a highly useful concept. The Nobel Prize in Chemistry went to Frederick Sanger of Cambridge University who analyzed the intimate structure of insulin using methods which Ingram employed in the study of abnormal hemoglobins (¶ 149).

Youth is a striking feature of these laureates. Lederberg is 33; Sanger is 40.

Twice previously the Nobel Prize in Medicine and Physiology has been awarded to workers in the field of genetics. In 1933 Thomas Hunt Morgan (1866-1945) received the award "for his discoveries concerning the function of the chromosome in the transmission of heredity." Morgan studied the exceptions to Mendel's second law (independent assortment) and their explanation in linkage and crossing-over. In 1946 Hermann Joseph Muller (1890-) was awarded the prize "for his discovery of the production of mutations by means of x-ray irradiation."

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55. Hirschhorn described the various centers of Western Europe where research in human, medical, and clinical genetics is going on.

56. A "Multiple Birth Roster" was initiated on Jan. 1, 1958, by the New York City Department of Health under the direction of Dr. Harold Jacobziner. All multiple births involving at least two live infants will be included. Identifying, demographic, and pregnancy information from the birth certificate will be put on a punch card. The roster will be kept up to date with respect to adoption, death in the first year, and data turned in to the roster by researchers using it. Students of human genetics may use the roster if certain stipulations are met.

II. HISTORY

(*See also ¶'s 5, 31, 54.*)

57. Nineteen fifty-eight marked the fiftieth year after two landmarks in the history of human genetics. In 1908 Garrod delivered his famous Croonian lecture, "Inborn Errors of Metabolism," in which the foundations for biochemical genetics were laid. Also in 1908 Hardy, a British mathematician at the University of Cambridge, and Weinberg, a physician in Stuttgart, independently formulated the concept which has since been known as the Hardy-Weinberg law and which is the foundation of population genetics.

The *American Journal of Human Genetics* took note of the Garrod semicentennial by reproducing a portrait of Garrod (March), by publishing a series of reviews of Garrod's "Big Four" of biochemical genetics (cystinuria, alkaptonuria, albinism, and pentosuria) by W. Eugene Knox and by a note on Garrod by his friend and colleague at Oxford, Rudolph A. Peters. The historical develop-

ments in the field of biochemical genetics were particularly well reviewed by Knox, although the discussion was confined to the four entities mentioned. Worth-while historical details were presented in many of the reviews of individual diseases.

58. Wilhelm Johannsen (1857-1927) of Copenhagen, creator of the terms "gene," "phenotype," "genotype," and "pure line" was described, with portrait, by Winge. Johannsen's *Elemente der exakten Erblichkeitslehre* (1909) went through several editions.

59. Burch provided an interesting biographical account of Carl Friedrich Gauss (1777-1855), the mathematical genius whose name is sometimes attached to the "normal" distribution curve.

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60. Richard Goldschmidt, former chief of the Max Planck Institute for Biology in Berlin-Dahlem and emeritus professor in the University of California, died April 12, 1958. Goldschmidt was a student of physiologic genetics. He invented the term "phenocopy."

Ochoa and Kalckar evaluated the contributions of Gerty K. Cori (who died Oct. 26, 1956), including those to biochemical genetics. Kalckar pointed out that glycogen storage disease was the first hereditary disorder in which the defective enzyme was identified.

III. GENERAL GENETICS. SELECTED PUBLICATIONS

61. Russell, Russell, and Kelly demonstrated in mice that the specific locus mutation rates are lower with chronic gamma irradiation of spermatogonia than with acute x-ray exposure. Difference in quality of irradiation (gamma versus x-ray) cannot account for the results, which seem to contradict the classic findings for Drosophila spermatozoa in which the mutation rate is proportional to total dosage and independent of the intensity with which the irradiation is applied. The dose-rate effect, however, is not observed in experiments with mouse spermatozoa; there is, therefore, no fundamental disagreement of the mouse and Drosophila data. These workers point out that the data do not necessarily contradict the linearity concept and the view that there is no threshold for radiation effect. The possibility that some mutations are reparable or preventable would account for the findings without contradiction of the nonthreshold concept.

62. In a survey article entitled "Some Recent Advances in Molecular Biology," Perutz reviewed work on the structure and replication of DNA, RNA as the link between DNA and protein, and the molecular structure of proteins such as insulin, myoglobin, and hemoglobin.

63. Robinson provided a comprehensive treatise on the genetics of the rabbit which should be useful in connection with comparative genetic pathology since hereditary rabbit diseases are discussed.

Fortuyn described, in mice, nongenetic sib resemblances with regard to life-span and with regard to other quantitative characters: footlength and number of tailrings. Environmental factors can, he points out, result in closer resemblance among sibs than among sibs and parents even in isologous strains. He pointed to some data in human genetics as being perhaps partially explicable on this basis: Penrose (1948) found for age of onset in myotonia dystrophica a correlation coefficient of $+0.32 \pm 0.13$ for affected parent with affected child but one of $+0.66$ between affected sibs. Penrose suggested an alternative possibility: the allelic partner of the dominant dystrophia gene, inherited from the unaffected parent, may have several forms and the normal allele may be different in parent and child but must always be the same in sibs.

64. Penrose described a highly ingenious mechanical model of self-reproduction. In 1946 Von Neumann, the mathematician, had suggested the possibility of such a model. The model was proposed as an analogue of replication in DNA.

65. The genetics of fungi (Wheeler) and of bacteria (Ravin) was reviewed in a useful manner.

66. Sheep fall into three groups as to hemoglobin type: AA, AB, or BB. There are two groups as far as potassium content of whole blood is concerned (Evans, Harris, and Warren). Polymorphism in the potassium and sodium content of the red cells also occurs in sheep. Beta-globulin polymorphism is demonstrable in cattle, sheep, and goats (Ashton and McDougall; Ashton) and hemoglobin polymorphism in mice (Welling and van Bekkum; Rosa and associates).

67. Benoit and colleagues extended their observations on change in beak color of Pekin ducks injected with DNA from Khaki Campbell ducks. F_1 ducks from injected females showed inhibition of the usual yellow pigmentation (1957). The latest report indicates the same finding in another F_1 generation and in F_2 issue from the F_1 generation.

IV. HUMAN GENETICS, GENERAL CONSIDERATIONS

The Human Chromosomes.—

68. Further results of tissue culture techniques in the study of human genetics at the cellular level have appeared from Puck's laboratory (Tjio and Puck). The chromosomes from several different normal organs of 13 different humans showed no variations in morphology or number except for sex differences and a small incidence of polyploidy. Furthermore the chromosome number and morphology in normal human tissues remained constant after more than 5 months of continuous, rapid growth. Tjio and Puck suggest that the individual chromosomes can be characterized on the basis of their size, position of the centromere,

and possession of a satellite. According to these features they assign the chromosomes to one of 3 groups. Pointing out that the X chromosome is about 3 times as large as the Y chromosome and the chromosomal volume of the female cell about 4 per cent greater than that of the male cell, the authors ask whether the substantially richer genetic endowment of the female may be responsible for the sex difference in longevity (see Scheinfeld). Furthermore, they predict sex differences in radiation effects.

Kodani found in 15 Japanese testes 9 cases of 46 chromosomes, 1 of 47, and 5 of 48. In 8 testes from white men there were 7 with a chromosome count of 46 and 1 of 48. These findings are in disagreement with those of all other workers (e.g., Ford, Jacobs, and Lajtha). The latter workers, using short-term bone marrow cultures, found the diploid number in 22 persons to be 46. Females were found to have 4 small acrocentric ("terminal centromere") chromosomes and males had 5; the fifth is the Y chromosome.

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Dominance.—

69. Two publications, one by Gordon Allen and the other by Allison and Blumberg, emphasized the realignment of thinking about the terms *dominant* and *recessive.* At least three factors have been responsible for redefinition: (1) discovery of instances in which blending or intermediate expression of unit characters occurs in heterozygotes, (2) demonstration that careful study may reveal slight abnormality in persons heterozygous for a "recessive gene," and (3) discovery that some diseases in man are not the same when the gene is in heterozygous state as when it is homozygous. Allen pointed out that Mendel applied the terms *recessive* and *dominant* to characters, not genes.* He suggested, furthermore, that confusion could best be avoided by returning to this practice. Perhaps unwittingly, Allison and Blumberg create the impression that Stern, and Neel and Schull do not appreciate the true significance of the terms recessive and dominant, or, at least, do not make it clear in their textbooks. The few words quoted from each, out of context, certainly give this impression. The point made by the authors of this article, although of no great genetic sophistication, is a useful one for the clinical audience for which the *American Journal of Medicine* is intended. Furthermore, the authors collected all available information on conditions which are known to have a different state in the rare homozygous from that in the less rare heterozygous state and which cannot, therefore, be considered true dominants. Theories of dominance, examples from lower animals, and other interesting aspects are presented.

In this review attempts will be made to use *dominant* and *recessive* only to describe the behavior of a trait. There need be no confusion as to what is meant. There is much to be said for stating that a given gene is expressed in the heterozygous state or only in the homozygous state. However, no simple way around this cumbersome phraseology is immediately evident.

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*Mendel wrote as follows: "Henceforth in this paper those characters which are transmitted entire, or almost unchanged in the hybridization and therefore in themselves constitute the character of the hybrid, are termed the *dominant*, and those which become latent in the process *recessive*."

Man and His Environment.—

70. Neel produced a philosophical editorial in which he pointed out the extraordinary rate at which man's environment has changed in a relatively short period, and, on the other hand, the genetically imposed limitations to adaptation to change. He implies that many "modern diseases" are the result of our evolution not keeping up with our environmental changes. In fact we hamstring evolution by many of our medical measures.

> Man, who is without doubt an enormously adaptable organism, is being thrust at a constantly accelerating rate into environmental situations in which he has previously not been tested . . . . In this highly competitive world of today there is, in my opinion, a real possibility of creating a culture in which, without being given the time in generations for the necessary genetic adjustments, a large fraction—perhaps a majority—of the population cannot function without developing a variety and profusion of maladaptation syndromes. By maladaptation syndromes I refer to such diverse entities as the so-called stress diseases, severe psychoneurosis, or early atherosclerosis and coronary artery disease . . . . This problem will be of greatest magnitude where large areas, such as Africa, make the cultural transition relatively rapidly. The apparently greater frequency and severity of hypertension in the American Negro may be an illustration.

Polymorphic Systems in Man (*see also* ¶'s 26, 27, 90).—

71. Grubb and Laurell (1956) found in the serum of many normal individuals a gamma-globulin which inhibits the agglutination of sensitized Rh-positive type O red cells by serum from a patient with rheumatoid arthritis. The trait has been referred to as the Gm (for gamma) factor. Linnet-Jepsen, Galatius-Jensen, and Hauge found that of 1,084 unrelated individuals 55.63 per cent had the factor. The two phenotypes were referred to as Gm (a+) and Gm (a−). They think there are three genotypes (with the frequencies indicated): Gm^aGm^a (0.1115), Gm^aGm (0.4448) and GmGm (0.4437). The frequency of the Gm gene was estimated to be 0.666.* Newborn infants have the mother's Gm phenotype; they develop their own along with other gamma globulins later in the first year of life.

72. Polymorphism in the human serum beta-globulins and their genetic control has been demonstrated by Horsfall and Smithies. In animals genetically determined beta-globulin types are found also (see ¶66). The beta-globulins are involved in iron transport; hence, the alternative designation, transferrins.

Study of the genetics of the haptoglobins by Galatius-Jensen amply confirmed the genetic theory of Smithies and Walker. Galatius-Jensen also reported on rare phenotypes in the haptoglobin system. In two generations of one family he discovered 8 cases of ahaptoglobinemia, for which hemolytic disease could not afford an explanation. In a second family a previously undescribed haptoglobin type occurred in 3 individuals. Allison, Blumberg, and ap Rees found ahaptoglobinemia in 2.7 per cent of 218 British persons. Again, hemolysis was

*See footnote to ¶ 26.

presumably not present. In addition to finding cases of idiopathic ahaptoglobinemia, Siniscalco and colleagues found, in 3 families, 5 children who were 2.2 from 1.1 mothers. Modifiers or other genetic complexities may result in minor exceptions to the Smithies-Walker hypothesis. The relative frequencies of the three haptoglobin types, 1.1, 2.1, and 2.2, are, in European populations about 0.16, 0.48, and 0.36, respectively (see ¶ 26).

73. The inheritance of the PTC (phenylthiocarbamide) taste character in man was analyzed by Das in 126 families in India (see ¶ 90).

Kalmus gave a semipopular presentation on "the chemical senses."

Brandtzoeg Merton presented evidence that the ability to taste PTC is inherited as a dominant. There was no clear linkage with any one of 9 blood group systems.

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Yang Chün and colleagues tabulated the frequency of color blindness in China based on 55,973 tests, of which 13,071 were tested by these workers. Most of the tests were performed using Ishihara's pseudoisochromatic plates. The frequency in males was 4.99 per cent and in females 0.81 per cent. However, the corresponding figures for the authors' own series were 5.22 per cent and 0.47 per cent.

The large remaining areas of ignorance in connection with color-vision are clear from the paper of Graham and Hsia and the critique of same by Walls.

74. Earle and his colleagues in Chicago and Boston, and Knedel in Germany described a unique human serum albumin inherited as a dominant heterozygous character. Seemingly an allele of the "normal albumin gene" is responsible for a different albumin that migrates more slowly than normal albumin. The electrophoretic pattern shows a double albumin peak. Earle and his associates suggest the designations albumin A (normal) and B (anomalous). Albumin B averaged 57 per cent of the total serum albumin. No immunologic differences of albumin A and B could be demonstrated. Albumin B was demonstrated in 25 members of three generations by Earle. As in the case of the Gm serum groups, the haptoglobin groups, and the beta-globulin variants, there was no associated disease. Knedel found a "double albumin" in 5 members of three generations in one family and in 3 siblings in another family.

Trends.—

75. Carter and Harris reviewed experimental and human genetics in Holzel and Tizard's *Modern Trends in Pediatrics.* They summarized the lines along which they expect human genetics to develop in the next decade. Here are some of them:

1. An increased understanding of the biochemical action of genes. The determination of the specific disturbances in metabolism due to gene mutations.

2. An extension of twin studies (a) to include conditions in which genetic factors in causation are not yet determined and (b) to identify the environmental factors responsible for discordance in monozygotic twins.

3. Extension of family studies into the second generation in conditions such as Hirschsprung's disease and tetralogy of Fallot, which are now being treated with sufficient success to permit reproduction.

4. The use of genetic studies to differentiate disorders which at first sight cannot be distinguished clinically.

5. The development in association with family studies of methods of detecting "carriers" of mutant genes: heterozygotes for recessive genes, heterozygotes for dominant genes which give clinical expression late in life, persons with the genetic predisposition for a disease of mixed genetic and environmental causation.

6. Determination of the protective environmental factors in persons who are known to have the requisite genotype but who are clinically normal.

7. Further linkage studies relating pathogenic mutations to known markers.

8. Further study of cousin marriages to determine the average number of potentially pathogenic genes carried in heterozygous state and the part played by recessive genes in what now appears as nonspecific fetal and infant mortality.

Miscellaneous.—

76. Jean Sutter of Paris published his important study of consanguinity in three French *départements*. Displaying his usual strong historical sense, Sutter introduces his report with the history of man's concern over the effects of consanguinity. He described the famous controversy which started in France in 1856 when Ménière read a paper at the Academy of Medicine maintaining that deaf-mutism results from consanguineous matings. It was Sutter who rediscovered the important body of data on the effects of consanguinity, collected in this country by Bemiss for the American Medical Association a century ago.

Alström provided a historical analysis of first cousin marriages in a social isolate, the Swedish nobility. A figure as high as 13 per cent was arrived at for high nobility.

In a religious isolate in midwestern United States Hammond and Jackson found that in 627 marriages of descendants of a Swiss couple who immigrated in 1853, there were 4.1 per cent first cousin marriages or closer, and 21.5 percent second cousin marriages or closer, contracted between 1850 and 1949.

Schull presented data collected in Japan from 1948 to 1956, bearing on the question of the influence of consanguinity on sex ratio, the frequency of malformations, viability, and other factors. As in other parts of the world the frequency of consanguineous marriages "is clearly on the decline." No influence on sex ratio was observed. The frequency of major congenital malformations was, however, significantly increased. A considerable portion of the increase involved complex or multiple major malformations. An increased death rate in the offspring of consanguineous marriages was observed. The effect was clearly demonstrable in the first 9 months of life and in one of the cities studied (Hiroshima), after the first year of life, as well. There was no definite effect of inbreeding on the length of the interval between cohabitation and first recognizable pregnancy, to suggest early fetal loss. Unique features of the design and

conduct of the study were considered to be (1) its prospective orientation, (2) the size of the sample, and (3) the use of trained observers, usually physicians, in collection of the data.

77. von Sydow and Rinne described monozygotic, monochorionic, diamniotic twins who displayed marked differences in birth weight and hemoglobin values. The differences persisted until at least 10 months of age. In utero starvation of the small twin was postulated. One of Price's "primary biases in twin studies" (1950) may be illustrated. Silver and Cunningham described male twins, one weighing 6 pounds, the other 2 pounds, 8 ounces. Zygosity was not studied. In fact, superfetation was the major consideration in their discussion.

Bulmer studied the twinning frequency among sibs of twins taking maternal age into account. No clear indication of increased twinning was discovered. (See ¶ 48).

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Twins are also discussed in ¶'s 32, 56, 77, 87, 91, 133, 165, 168, 190, 196, 257, 266, 273, and 287.

78. In Japan Matsunaga and Itoh studied differential fertility between different mating types according to ABO, MN, and Q blood groups. No indication of a selective force with respect to MN and Q was discovered. In the ABO mating types two opposing selective forces were found: (1) The frequency of abortions and of childless couples was higher in incompatible matings than in the compatible ones. Maternal-fetal incompatibilities seem the probable basis. This selection would operate to reduce genes A and B and increase O. (2) Matings in which the father was blood group O had significantly lower fertility than those in which neither parent was group O. The effect is to favor the A and B genes in the population. The biologic basis for the second selective force is not evident.

79. Transplantation genetics in man promises to become a field of great theoretical and practical interest (Ferrebee). The transplantation of bone marrow into leukemic persons and of kidneys into persons with chronic nephritis is being explored. Murray, Merrill, and Harrison reported on kidney transplantation in 7 pairs of identical twins. One of the recipients went through a pregnancy successfully 1½ years after transplantation. In one recipient, glomerulonephritis developed in the transplanted kidney leading to death and the same may have occurred in a second recipient. In the Third Tissue Homotransplantation Conference (Rogers) sponsored by the New York Academy of Sciences the immunogenetics of tissue transplantation was discussed in eight papers.

80. In Tanner's discussion of the place of human biology in medical education, genetics occupied a prominent place. Lancelot Hogben drew on his long experience with medical genetics and medical schools to write on "The Place of Genetics in a Contemporary Curriculum of Medical Studies." He points out that genetics can make no claim on a niche in the curriculum on the basis of any

usefulness in connection with what he terms the quasicompulsive group of genetic disorders. It is in the diseases of multifactorial causation that genetics has its most important claim. Hogben digressed to discuss *etiology* and *cause*.

> During the first 30 years of my professional career, I never used the word *cause* in a lecture; but I have now lapsed into doing so, because the inherent danger lies less in the use of the noun than in the use of the article which precedes it. While we can never—except elliptically when the context makes the limitations explicit—speak with propriety about *the* cause of an occurrence, we can speak of *a* cause without clouding the issue. Thus we rightly conceive its province only if we regard aetiology as the disclosure of a *causal nexus* in contradistinction to the identification of a singular cause.
>
> In short, the plea I am advancing is that some sort of instruction in genetics is an essential ingredient of the medical curriculum less because of its direct usefulness as a guide to preventive action, such as compulsory sterilization or precautionary measures for putative parents with serum incompatibilities, than because it is an indispensable prerequisite to a comprehensively rational attitude to aetiological issues.

81. Tanner, Whitehouse, and Powell have devised a material they call "Armadillo," which consists of a large number of lead scales arranged in a manner similar to that of the elements of Roman armor. Now commercially available, the material is recommended for clothing to shield the gonads from radiation exposure.

The Advisory Committee on Biology and Medicine of the U.S. Atomic Energy Commission issued an explanatory statement on radioactive fallout. The report of the United Nations Scientific Committee on the effects of atomic radiation is likely to be a standard source of information for many years.

In reviewing the hazards of carbon-14, Totter and associates pointed out that, when the C^{14} atom in DNA decays to N^{14} by emission of a beta particle, a mutation might occur in either of two ways: (1) as a radiochemical change in DNA by impact of the beta particle, or (2) from the transformation itself. Pauling also wrote an estimation of the genetic significance of C^{14} created from the nitrogen of the atmosphere by neutrons emitted in atomic exposures. The half-life of C^{14} is 5,600 years. He calculated that one year's testing could, through the agency of C^{14}, be responsible for 55,000 gross defects, 170,000 stillbirths and childhood deaths, and 425,000 embryonic and neonatal deaths per year. (There is an unknown amount of overlap in these categories.)

An editorial in *Lancet* emphasized that the main source of radiation exposure is clinical x-ray. Work in mice by Carter suggests that in adults protection of the male gonad may be more important than protection of the female gonad. Whereas in the female the germ cells are in the less sensitive oocyte stage in adults, in males spermatogonial stages are present. Work in mice suggests that the germ cells of the postnatal male are as much as 10 times more mutable than those of the adult female.

82. Vogel reviewed the subject of delayed mutation and germinal mosaicism in man, with particular regard to the "split-hand syndrome" (ectrodactyly). Charlotte Auerbach (1946) of Edinburgh found in studying nitrogen mustard

mutagenesis in *Drosophila melanogaster* a phenomenon that she interpreted as indicating that mutagens could induce "premutation"—an unstable form of allelomorph which could revert to the stable wild type allelomorph or go on later to an equally stable mutant allelomorph. The premutant allele had the wild phenotype. The pedigree pattern showed in F_1 some complete mutants from a treated parent (P_1) and other offspring which although normal produced a small proportion of affected offspring. In F_2 and other generations from the affected offspring the mutant gene behaved in a strict Mendelian manner. Auerbach (1956) proposed that a family with ectrodactyly reported by John B. Graham and C. E. Badgley of Chapel Hill might illustrate delayed mutation.

Germinal mosaicism may result in a rather similar pedigree pattern. The occurrence of a somatic mutation involving part of the germinal cells of a parent (at some stage in his embryonic development) can have the result that two or more offspring from two normal parents are affected by a dominant trait which in the subsequent generations behaves in a simple Mendelian manner. Reed and Falls (1955) presented a pedigree of aniridia which might, they thought, represent germinal mosaicism and Mackenzie and Penrose (1951) suggested the same explanation in a pedigree of ectrodactyly. The phenomenon has been several times observed in other mammalian species.

Both delayed mutation and germinal mosaicism are indistinguishable from the effects of reduced penetrance. Since few dominant traits are fully penetrant, Vogel concluded that it is impossible to establish delayed mutation or germinal mosaicism as facts in man. Further inquiry revealed that a tradition of a forebear with an anomalous hand had been passed down in the family reported by Graham and Badgley.

83. The ultrastructure of the human sperm was studied by Schultz-Larsen using electron microscopy. He demonstrated that the head contains an acrosome, as in other species; this organelle may be involved in assisting entry of the sperm to the egg by enzymatic activity.

In a popular article with the intriguing title "The Control of Sex," Gordon described experiments in influencing the sex ratio through electrophoretic separation of sperm.

V. METHODS

A. Statistical.—

84. Strobel and Vogel estimated mathematically the precision with which it is possible to evaluate the trend in time of the spontaneous mutation rate in man. The question of what size of population would be necessary to detect a change in mutation rate was examined.

85. Simpson demonstrated the feasibility of estimating linkage on an electronic digital computer. In 1953 C.A.B. Smith suggested this method for

facilitating the time-consuming analyses. A program for analysis of data from two-generation families was described.

86. Morton applied the maximum probability theory of Fisher to segregation analysis in human pedigree data, that is, for arriving at an appropriate genetic hypothesis.

Knox derived the algebraic expressions for the expected genotype frequencies for various relatives of a propositus affected by a sex-linked recessive trait. Using these formulas he derived from pedigree data an estimate of the gene frequency of color blindness. He points out that there are two other methods: (1) The incidence in males, designated by Knox as g, is also the gene frequency. (2) The ratio of affected females to affected males is also the gene frequency. (If $M = g$, then $F = g^2$ and $F/M = g$.) The new method based on pedigree data yielded an estimate which checked well with the results of the other two methods. He then turned (in a third paper) to congenital pyloric stenosis. Any etiologic hypothesis must, he pointed out, account for the facts (1) that males are affected 4 or 5 times more often than females, (2) that there is a familial concentration in parents, sibs, and offspring, (3) that the incidence declines with increasing birth rank, and (4) that there are more females than males among the sibs of parents of affected children. This is true for both parents of affected girls but only for the mother's sibs in the case of affected boys. Several of these features suggest X-borne inheritance. If indeed X-linked, since the sex ratio is the gene frequency ($F/M = g^2/g = g$), then pyloric stenosis might be determined by a gene with a frequency of 0.20. This would mean that 1/5 of males and 1/25 of females are susceptible, or about 120/1,000. Since the incidence is about 3/1,000, penetrance could, on the basis of this hypothesis, be only about 1/40.

Knox pointed out that sex linkage could account for (1) the sex ratio, (2) the sex ratio among parents' sibs, (3) the sex ratio of affected parents of affected children, and (4) ratio of affected paternal first cousins to affected maternal first cousins. However, the sex-linkage theory is impaired by (1) the paucity of expected FF ("two female") affected sib pairs, (2) the failure to observe the expected 1:1 sex ratio of affected children of males, and other findings. "Indeed, it now seems necessary to replace pyloric stenosis in a class with those other diseases for whose curious ancestor-patterns we likewise have no ready explanation, and to consider other causes."

87. Curt Stern showed that "with complete ascertainment, in populations with twin material unselected except for the presence of a specific trait (1) the ratio of ascertainable MZ to DZ twin pairs lies between ½ and 1 of the ratio in the general population and (2) the ratio of all ascertainable twin pairs to the total number of individuals lies between one and two times that found in the general population."

88. The methodology involved in establishing familial aggregation of a disease such as breast cancer was well reviewed and illustrated by Anderson and his collaborators in their study of breast cancer (¶219).

B. Biochemical.—

89. Chromatography and electrophoresis, techniques which have permitted many of the recent advances in biochemical genetics in man, were discussed in a useful manner by Jonxis.

C. Others.—

90. Kalmus demonstrated that PTC taste testing can be improved by combining testing for quinine-tasting threshold.

91. The diagnosis of zygosity in twins was the subject of a highly useful analysis by Juel-Nielsen, Nielsen and Hauge. They estimate that by the use of sex, eight blood groups (A_1A_2BO, MNS, Rhesus [with five sera], P, Lewis, Kell, Lutheran, and Duffy) and two serum protein groupings (haptoglobin and Gm) it is possible to establish dizygosity in about 98 per cent of all dizygotic twin pairs.

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VI. BIOCHEMICAL GENETICS

92. General aspects. Driscoll and Hsia provided a review of "The Development of Enzyme Systems During Early Infancy." There are many genetic implications in the review: defect in the glucuronosyl transferase enzyme system, involved in bilirubin excretion, in rats and man; defect in galactose metabolism in galactosemia; fetal hemoglobin in the newborn; methemoglobinemia; glucose-6-phosphate dehydrogenase deficiency; acatalasemia; ceruloplasmin deficiency; and others.

In reviewing biochemical genetics Kalckar presented some very interesting and important information and concepts; phenotypic expression of genes in the haploid gametes and their potential usefulness in artificially selecting against genetic biochemical errors; the possibility that some hereditary metabolic diseases (? e.g., gout) are not simple enzyme blocks; the questions of whether the individual heterozygous for a "recessive" biochemical disorder possesses two populations of enzyme; etc.

In an editorial entitled "Genetics and Glycolysis" Bessman discussed *inter alia* pentosuria, galactosemia, glycogen storage disease, hereditary spherocytosis, and primaquine sensitivity.

93. Agammaglobulinemia (Gitlin and Janeway). Zelman and Lewin reported on a 25-year-old male with agammaglobulinemia complicated by recurrent pyogenic infections, a spruelike syndrome, and reticuloendothelial hyperplasia of the spleen. A genetic basis was suggested by the finding of hypergammaglobulinemia (sic) in both parents. Congenital basis in the propositus was suggested by the association of congenital anomalies: osteochondroma of the humerus, hyperostosis calvariae diffusa, spina bifida occulta, "an independent apophysis of the posterior tubercle" of the atlas.

Bouton and colleagues reported, from a sibship of 7, of whom the grandparents were first cousins, a girl with agammaglobulinemia and bilateral bronchiectasis, a boy who had died at 10 months of bronchopneumonia after suffering from respiratory infection from birth, and 2 boys with hypogammaglobulinemia.

94. Albinism. In reviewing the subject Knox emphasized our ignorance of the details of pigment formation. Presumably the defect in albinism involves the enzymatic conversion of tyrosine to melanin. Knox also threw interesting light on the controversy between the Mendelists and the biometricians in the early part of this century. Garrod's remarkable insight in classifying albinism as an inherited defect in an enzyme step in pigment formation is all the more interesting and significant when one reads the following in the monograph on albinism by Pearson, Nettleship, and Usher (1911): ". . . the ultimate difference between the normally pigmented individual and the albino will be found after all to be one of *structure*. It is easier to grasp the influence of a difference of genetic constitution on structure than on chemical process." Garrod's concept of biochemical genetics dating from at least a decade before had failed to penetrate the biometricians.

Furthermore, Pearson as Galton's successor seems to have tried to corroborate his mentor's views on heredity. He and his collaborators, after lumping together all forms of pigmentary disturbance with pigment lack (both hereditary and acquired types!) concluded that the data could not fit a simple Mendelian hypothesis: "As we have seen in the course of this work albinism is a graded character, and we have every reason to believe that both in man and dogs separate grades are hereditary. . . . Mendelism is at present the mode—no other conception of heredity can even obtain a hearing. Yet one of the present writers at least believes that a reaction will shortly set in, and that the views of Galton will again come by their own."

Sorsby amassed evidence to suggest that Noah was the product of a consanguineous, possibly incestuous, mating and was an albino.

95. Alkaptonuria was reviewed comprehensively by Knox. He expressed doubt that there is a dominant form of the disease. Many if not all the pedigrees which have been presented as instances of such inheritance, could he thinks, be explained on the basis of mating of affected individuals with heterozygous carriers, the frequency of which may be as high as 1 in 200. In this connection the pedigree reported by Khachadurian and Feisal is of interest: there were probably affected individuals in four generations. However, there was consanguineous marriage of certain of the affected persons in the family, which lived in an isolated community. Pagan-Carlo and Payzant analyzed the radiographic changes in alkaptonuric osteoarthritis, and LaDu and collagues reviewed the subject. In another paper, LaDu and colleagues reported that no homogentisic acid oxidase activity could be demonstrated in the liver of one patient. The lack of activity was shown not to be due to the presence of an inhibitor or the absence of any known cofactor.

96. Cystinosis. Cogan and colleagues in the first reported case of cystinosis in an adult demonstrated that characteristic crystals were present in the sternal marrow but not the skin and that the conjunctival crystals had the x-ray diffractometric characteristics of cystine. The patient was of normal physique and had no renal disturbance. Worthen and Good gave a good review and presented affected sibs; Weinberg presented the clinical and pathologic features in a 23-month-old child.

97. Cystinuria. Knox reviewed the subject comprehensively. Although Garrod included cystinuria among his inborn errors of metabolism, it has finally been established that it is not an enzyme defect involving the metabolism of cystine but rather a defect in the renal tubular reabsorption system. Garrod's concept of inborn error was so strong that recognition of the renal mechanism was relatively late in coming. (Similarly, the Dalmatian coach hound is unique among dogs by excreting uric acid, not because he lacks uricase, which he in fact has, but because his renal tubule fails to reabsorb uric acid.) The Garrodian inborn error of metabolism can easily be stretched to include defects of the renal tubule transport mechanisms.

Two variants of cystinuria have been delineated. In the more common Type I (about two-thirds of families) there is a sharp distinction between cystinuric and normal individuals, both parents are normal, there is an increased rate of parental consanguinity, and the proportion of affected sibs is that expected of a recessive. In Type II, individuals who are presumed homozygotes are indistinguishable from the homozygotes of Type I—both excrete cystine, lysine, arginine, and ornithine and form renal stones. However, in Type II the heterozygote is identifiable by an increased excretion of cystine and lysine at intermediate level. The heterozygote usually does not form stones. The genes for the two forms of the disease may be allelic. Alternatively, there may be modifying genes in some families determining the occurrence of one form rather than the other. Becker and Green could demonstrate no defect in the incorporation of cystine and lysine by cystinuric leukocytes as compared with normal leukocytes.

Cystinuria is not to be confused with cystinosis which probably is a systemic enzyme defect with cystine deposition in the tissues and the multiple features referred to as the Lignac-de Toni-Fanconi syndrome.

98. In *galactosemia* (Guest; Jacobson) the galactose tolerance test has some risk of aggravating the damage to the brain and other tissues. However, early diagnosis is desirable so that milk can be withheld from the diet promptly. Schwarz and colleagues in Manchester describe a safe test applicable to newborn siblings of persons with known galactosemia. The erythrocytes of cord blood are incubated in galactose. Galactose-1-phosphate accumulates in the cells of affected infants to levels much higher than in the normal. Management with a galactose-free diet instituted no later than the third month of life may result in normal development (Bennett).

99. Glucose-6-phosphate dehydrogenase deficiency. Primaquine-sensitive hemolytic anemia is a name sometimes used for this condition. It is established, however, that napthalene (Zinkham and Childs), sulfonamides, the bean of *Vicia faba* (Childs and associates; Zinkham, Lenhard, and Childs; Szeinberg, Sheba, and Adam, a), Furadantin (Kimbro and co-workers), and a number of other agents can cause the manifestations. The defect appears to involve glucose-6-phosphate dehydrogenase activity of the erythrocyte and to be inherited as a sex-linked recessive or intermediate (Childs; Szeinberg, Sheba, and Adam, a; Marks). Alving and his colleagues found abnormality in a second enzyme system; this may be a secondary effect. Zinkham and Childs described the case of a Negro woman who ate moth balls (naphthalene) during pregnancy because of perverted taste. It had very little effect on her but her male child was born with severe hemolytic anemia. Dawson and his associates also described naphthalene poisoning in newborn infants who were wrapped in moth-ball impregnated clothes. The thin skin of the infant, the immaturity of the glucuronide detoxifying mechanism for naphthol in the liver, and possibly the relative immaturity of the erythrocyte enzyme systems may predispose to intoxication. Methemoglobinemia is also a feature of these cases.

The gene frequency is much higher in Negroes than in whites. Gross and co-workers found a deficiency of erythrocyte glucose-6-phosphate dehydrogenase activity in 7.2 per cent of healthy Negroes and 1.3 per cent of healthy Caucasians. The causal relation to naphthalene intoxication and favism was confirmed. Sex linkage was also confirmed. Szeinberg, Sheba, and Adam (b) found the trait to be rare in European Jews; it was present in 11 per cent of oriental Jews (N = 279), and in 20 per cent of Iraqi Jews who are descended from the Judeans who were displaced by Nebuchadnezzar and who have remained particularly separate for about 2,500 years. It is of interest that this group had noted, even before the recent work on primaquine sensitivity that among Jews it is, for practical purposes, only the non-Ashkenazi who gets hemolysis from *Vicia faba*, sulfonamides, or idiopathic causes (? viruses).

100. Glycogen storage disease. Craig and Uzman described "a familial metabolic disorder with storage of an unusual polysaccharide complex." Clinically and pathologically the disorder suggested glycogen storage disease (for which reason it is discussed here) but the stored material was definitely not glycogen. They saw the disease in a brother and sister and a third unrelated child.

101. Hartnup disease. A case of "pellagra" in a 4½-year-old English child proved to be Hartnup disease characterized by a typical form of aminoaciduria (Henderson). Tryptophane is lost in the urine. In addition to the skin changes in exposed areas there was marked ataxia. A diet consisting largely of cornflakes and milk may have exaggerated the effects of the genetic defect. A high-protein diet supplemented with large doses of riboflavin and nicotinamide produced almost complete recovery, although some light sensitivity continued and the aminoaciduria persisted. There were by history no definitely affected

members of the family and the urine chromatograms, performed in 26 of the 31 living relatives, were normal.

102. Hemochromatosis appears to be an inborn error of iron metabolism. Sex influence at the phenotypic level is presumably due to iron loss in the female, through menstruation, pregnancy, and lactation. Pirart and Gatez studied 50 patients in 46 families. Four relatives of probands with hemochromatosis were found to have "complete hemochromatosis" and subclinical disease was judged to be present in 6. In the last group repeated bleeding performed for prophylactic purposes did not result in anemia. An affected mother and daughter were described. However, the authors seem to feel that the disease trait usually behaves as a recessive.

A more sophisticated approach was that of Debré and colleagues. They concluded that the biochemical defect is present in heterozygotes and that the disease has variable penetrance because of other influences on iron metabolism. Cases of hemochromatosis in juveniles resulting from consanguineous matings may represent the homozygous form of the disease. The authors found, among the sibs of 30 patients, 3 brothers who also had hemochromatosis. The history suggested the presence of hemochromatosis in some of the parents. The presence of the genetic defect was recognized by elevation of the plasma iron and an increased iron-saturation coefficient of siderophilin. In the sons (of probands) over 15 years of age the plasma iron level displayed a bimodality. The level of plasma iron was found to be age and sex dependent.

103. Hypophosphatemia. A large North Carolina family with vitamin D–resistant rickets due to familial hypophosphatemia was reported upon in detail by Winters, Graham, Williams, McFalls, and Burnett. This is one of the best available examples of a sex-linked intermediate or incompletely dominant trait: the hemizygous male is more severely affected than is the heterozygous female. (Other examples of this mode of inheritance are choroideremia [McCulloch and McCulloch, 1955] and "primaquine-sensitive" anemia [see ¶ 99].) The critical test of the hypothesis is provided by the progeny of the 7 hypophosphatemic fathers:

SEX OF PROGENY	AFFECTED	NORMAL	TOTAL
Males			
Observed	0	10	10
Expected if autosomal dominant	5.0	5.0	
Females			
Observed	11	0	
Expected if autosomal dominant	5.5	5.5	
Total			
Observed	11	10	21
Expected if autosomal dominant	10.5	10.5	

As would be expected with a sex-linked dominant, all the daughters and none of the sons of affected males are affected. (Linneroth and his colleagues studied what may be the same condition. In four families the inheritance seemed to be autosomal dominant. The same was probably the case in a further three families. Affected males had both affected sons and daughters. Genetic heterogeneity is likely.)

Such a carefully studied pedigree as that of Winters and colleagues reveals the ease with which a fallacious genetic hypothesis can be arrived at by examination of one or a few less extensively investigated pedigrees. In this disease autosomal dominant inheritance has been proposed (e.g., Mitchell and Mitchell, 1957), although the actual pedigrees are consistent with sex-linked dominant inheritance; specifically, affected offspring of affected males are all female. (Similarly partial sex linkage can simulate autosomal inheritance and a sex-linked recessive trait cannot be easily distinguished from a sex-limited autosomal recessive if the affected males do not survive to reproduce and if no method for identification of heterozygous carriers is available.)

The metabolic features are (1) hypophosphatemia, normal serum calcium, elevated serum alkaline phosphatase; (2) a probable gastrointestinal absorptive defect for calcium and phosphorus; (3) diminished renal tubular reabsorption for phosphate. Winters and collaborators feel incompetent to judge between two alternatives for the basic defect: (1) secondary hyperparathyroidism from diminished calcium absorption in the gut, or (2) an intrinsic renal tubular defect for reabsorption of phosphate. The Tm_p was depressed somewhat more in affected males than in affected females; however, the difference was statistically not significant in the small group studied. Linneroth and co-workers pointed out that an elevated alkaline phosphatase can be the only indication of the presence of the gene. This observation appears to argue against a primary renal tubular defect.

104. Methemoglobinemia. In 2 brothers with methemoglobinemia, Bono and Gamalero found clubbing of the fingers in the older. Vitamin C was effective. The parents did not show methemoglobin. There appear to be two main types of methemoglobinemia: (1) In one type there is an enzymatic defect of the red blood cell which renders it relatively incompetent in maintaining the reduced state of hemoglobin. There may be more than one form of this disease. Motulsky has identified a yellow protein which seems to be methemoglobin reductase, a diphosphopyridine nucleotide-dependent enzyme. This form of the disease is corrected by vitamin C or methylene blue; it is usually inherited as a recessive. (2) The second type should be classified as a hemoglobinopathy and will be so discussed (see ¶ 154). It is not correctable by any agent known and is usually inherited as a dominant.

Scott and Hoskins found that the reductase-deficiency form of methemoglobinemia is relatively frequent in Eskimos and Indians in Alaska. Depending probably on dietary intake of ascorbic acid, there were variations in expression of the trait. They described 9 cases in four interrelated sibships. The inheritance was apparently autosomal recessive.

105. Oxaluria (oxalosis). Godwin and colleagues described a 10-year-old boy dying of progressive renal failure from calcium oxalate renal stones, nephrocalcinosis, urinary tract infection. A brother had died, apparently of the same disease, at the age of 6 years. An aunt had a renal stone. At autopsy in the proband oxalate crystals were found in vertebral cartilage, pancreatic acini, pulmonary alveoli, myocardium, lymph nodes, adrenal cortex, hepatic arteriole, and thyroid. Oxaluria varies with glycine intake. Archer and co-workers suggest that there may be an abnormal conversion of glycine to oxalate, possibly because of a defect in the degradation of glycine through its major pathway. Shepard, Krebs, and Lee also concluded that the most likely source of oxalate was protein metabolism. Serum uric acid was elevated without azotemia and the output of oxalate was increased by a high protein diet.

The natural history of primary oxaluria is that described in Godwin's patient above. Archer and his associates could find no hyperoxaluria in the sibs, parents, cousins, aunts, uncles, and other relatives of 3 persons with proved cases. Among the deceased patients there was a story suggestive of the disease in a sib of one propositus. Since there were only 4 unaffected siblings in the three sibships the findings are not inconsistent with a recessive hypothesis. In this study and in reports in the literature no consanguinity has been encountered. Both males and females are affected. Concordance in one pair of twins is known.

106. Pentosuria. The excretion of L-xylulose in persons with chronic essential pentosuria is probably due to a genetic defect in the metabolism of glucuronic acid beyond the L-xylulose step (Hiatt). Knox points out that the possibility of a defect in a specific renal transport system for xylulose, although unlikely, has not been excluded.

107. Phenylketonuria (Meister). Berry and associates describe a filter paper test. Urine is absorbed on a strip of filter paper which is then dried and mailed to the laboratory. The test is performed at 4 to 6 weeks of age since phenylpyruvic acid may be absent earlier. (Woolf and co-workers suggest 21 days as the age for testing because of the severe effects on the brain in the first weeks of life if the disorder goes unrecognized and untreated.) The papers turn green immediately when a small drop of 10 per cent ferric chloride is added, if phenylpyruvic acid is present. Confirmatory chromatograms can be performed with bits of the same filter paper containing dried urine. The test can be used to follow therapy with low phenylalanine diet. Baird described a similar test.

Since essentially all food proteins contain about 5 per cent phenylalanine by weight, it is necessary to use synthetic mixtures of essential amino acids (Berry and his collaborators). Centerwall surveyed the commercially available preparations and offered several suggestions on the management of patients with phenylketonuria.

Knox and Messinger found higher plasma phenylalanine levels in 22 individuals heterozygous for the phenylketonuria gene than in 32 control individuals. L-phenylalanine was determined by the specific effect of phenylalanine decarboxylase of *Streptococcus faecalis* R followed by colorimetric estimation of the

phenylethylamine formed. There was, as with the phenylalanine tolerance test, overlap with the normal group. Individuals who could not be classified by one test could often be properly classified by the other.

Berg and Stern found that the iris of persons with phenylketonuria is, on the average, lighter in color than the iris of unaffected sibs—an extension of similar studies of hair color. Since phenylalanine inhibits mushroom tyrosinase, since the normal diet contains enough tyrosine to preclude the possibility that the primary defect in pigment metabolism is lack of tyrosine (derived from phenylalanine), and since phenylketonuric patients display a darkening of the hair when receiving a low-phenyalanine diet, the deficiency of pigmentation was attributed to inhibition of pigment formation by abnormal metabolites formed in phenylketonuria.

Følling of Oslo who first described phenylketonuria (1934) is still contributing to the subject.

Nishimura and associates found an intermediate metabolite of phenylalanine and tyrosine (2,5-dihydroxyphenylpyruvic acid) in the urine of patients with diffuse collagen diseases such as systemic lupus erythematosus. The material was *not* found in relatives or normal controls.

In a child with mental deficiency and recurrent episodes of edema Smith and Strang found alpha-hydroxy-butyric acid and phenylpyruvic acid in the urine. The former material produced an unusual pungent, unpleasant smell. Two biochemical defects were postulated: the familiar one of phenylketonuria and another leading to excretion of hydroxybutyric acid.

108. Porphyria (Beerman and Pastras). Klatzko reported the successful treatment of a case of *acute intermittent porphyria* with prochlorperazine. The mechanism of the beneficial effect is unknown but is probably similar to that of chlorpromazine (which like prochlorperazine has a phenothiazine nucleus).

Rimington defended Waldenström's classification of the porphyrias into three hereditary forms (acute intermittent porphyria, porphyria cutanea tarda and congenital porphyria) and symptomatic porphyria cutanea tarda secondary to alcoholic cirrhosis or exceptional causes such as porphyrin-producing adenoma of the liver.

Convulsions in acute intermittent porphyria were described (Finkelman). It was emphasized that with proper management recovery from complete respiratory paralysis is possible (Doll, Bower, and Affeldt). See Silverstein for a survey of neurological manifestations. AIP and pregnancy seem to have no influence whatever on each other (Tricomi). AIP was described in a mother and 2 children, confirming the previous impression of dominant inheritance (Seide).

In an American Negro, Galambos found the metabolic disturbance of *porphyria cutanea tarda* without skin lesions. Apparently even hyperpigmentation was absent. Large amounts of free porphyrins were demonstrated in the liver by biopsy; fecal and urinary porphyrin excretion was at a high level. No porphobilinogen was excreted. Here may be a situation similar to that in sheep: black sheep are resistant to the photosensitizing effects of porphyrins. However,

Holti and associates traced porphyria cutanea tarda through four generations of a white family and pointed out that skin lesions could be very mild. Constipation was frequent. They emphasized that there are two "hepatic" forms of porphyria—acute intermittent porphyria and porphyria cutanea tarda—and also the diagnostically important fact, pointed out previously by Rimington, that fecal porphyrin excretion is always elevated in these cases despite intermittently normal urinary excretion. Haeger also found, in 12 patients, that the porphyrin content of the stool is a better index of porphyria cutanea tarda than urinary excretion. On the other hand, he found that all 34 patients with acute intermittent porphyria excreted porphyrins in the urine and that two-thirds of them also excreted δ-aminolevulinic acid.

In the rare *congenital porphyria* (Chaudhuri), which has been found to be a disorder of the erythroblast (hence the alternative designation "erythropoietic prophyria"), Varadi described needlelike structures, probably crystals of porphyrins in the normoblasts and nonnucleated red cells. Splenectomy in this and the other reported cases was helpful. The associated hemolytic anemia and thrombocytopenia were cured. Because of diminished hyperactivity of the bone marrow, the rate of porphyrin production and perhaps the degree of photosensitivity were reduced. Congenital porphyria apparently identical to the disease in man was described in Holstein-Friesian and other cattle (Rhode; Nestel). It is called "pink tooth" by cattlemen. Photosensitivity, discoloration of the bones, and hematologic disturbances occur. In cattle and in man the disease seems to behave as an autosomal recessive.

Watson and colleagues concluded that the disease in Holstein cattle is fundamentally similar to human *porphyria erythropoietica*. Although in man porphyrin excretion is diminished, at least temporarily, by splenectomy, in one cow splenectomy had no effect. Interestingly, only white areas of the black-and-white cows display photosensitivity. This is a situation comparable to that in Negroes, who less often have photosensitivity or may display atypical skin changes such as scleroderma. Similarly white sheep have been strongly selected against in these parts of the world where the forage contains photosensitizing materials.

109. Pseudocholinesterase deficiency. Prolonged apnea after suxamethonium (succinylcholine, decamethonium) used as a muscle relaxant in anesthesia was related to a hereditary deficiency of pseudocholinesterase in the plasma. Apnea was corrected by the intravenous administration of pseudocholinesterase (Lehmann and Simmons). Fresh blood may be similarly effective. Lehmann, Patston, and Ryan concluded that the inheritance of plasma pseudocholinesterase level is determined by two allelic genes neither of which has dominance. The persons with very low levels appear to be homozygous for the "abnormal" gene whereas those with intermediate levels are probably heterozygotes. It is of interest that differences between horses and cattle in response to succinylcholine can be related to the pseudocholinesterase level: the horse, with a high enzyme level, recovers rapidly; the cow, with a very low level, recovers slowly (Stowe and associates). This is a genetic condition which like primaquine sensitivity

(¶ 99) remains unexpressed unless an environmental agent is present. Unlike primaquine sensitivity, no population is known in which the gene has appreciable incidence.

110. Although not proved to be heritable and not proved to be a syndromal association, *sucrosuria*, hiatus hernia, and mental deficiency have been observed together in at least 15 children (Woodruff). Sucrose is normally hydrolyzed in the intestine to glucose and fructose. Ordinarily it is not absorbed as sucrose. If it is absorbed it is excreted largely unchanged in the urine. Ordinary reducing tests will not demonstrate sucrose in the urine. It is necessary to heat the urine for 10 minutes after adding a few drops of concentrated acid; the Benedict test on the urine will then be positive. Is sucrosuria a genetic defect of intestinal absorption?

111. Wilson's disease (Gitlin and Janeway). The effectiveness of penicillamine in promoting copper excretion was confirmed (Osborn and Walshe). Finby and Bearn suggested on the basis of 20 patients, of whom 14 showed skeletal changes, that the abnormalities can be put into two classes: (1) Osteomalacia and Milkman pseudofractures can be explained on the basis of Fanconi syndrome with phosphorus loss which results from the renal tubular lesion. (2) Bone fragmentation, precocious osteoarthritis, and degeneration of cartilage may be more directly related to the accumulation of copper in the affected tissues. Tests of the latter hypothesis are under way.

Fister, Boulding, and Baker described a dramatic response to penicillamine in a moribund patient with *Wilson's disease*, in which BAL and calcium versenate had been ineffective.

Brage thinks aminoaciduria is a primary defect and not secondary to a disorder of copper metabolism (see ¶ 34).

Morell and Scheinberg succeeded in preparing from ceruloplasmin an apoprotein which would combine reversibly with copper. Firm support is here provided for the role of ceruloplasmin in copper binding, transport, and release. Neale and Fischer-Williams found a definitely low serum copper in only 5 of 48 relatives of patients with Wilson's disease.

Miscellaneous: 112. In writing about *idiopathic hypercalcemia of infancy* Fellers and Schwartz suggested that "this disease [is] in the rapidly growing list of inborn errors of metabolism, or molecular disease." Actually they and others seem to have no evidence whatever to support a genetic hypothesis.

113. France and Tolleson observed 2 brothers in whom *potassium depletion* was a major disability. Symptoms began at the age of 22 years in both. A specific renal tubular defect was postulated. An aldosterone-secreting tumor could not be completely excluded.

VII. CONGENITAL MALFORMATIONS

114. Neel provided a thought-provoking discussion of congenital defects. On the basis of his study in Japan he concluded that only 10 per cent can be

explained on the basis of completely penetrant single genetic factors with a simple genetic behavior and only 10 per cent can be explained by maternal illness, malnutrition, etc. Neel thinks it unlikely that much of the remaining 80 per cent is due to dominant mutations, poorly penetrant dominant or recessive genes, *or* environmental influences. He suggests that "a significant fraction of human congenital defects are the segregants (phenodeviants) resulting from the existence and functioning of complex (multilocal) genetic homeostatic systems, of the type particularly discussed by Lerner" (*Genetic Homeostasis*, 1954). He implies that through the action of mutation and natural selection human populations have built up balanced polymorphic systems consisting of polygenes existing in heterozygous state and determining normal development. A congenital defect would then result when the proportion of heterozygous loci drops below a certain threshold. The observation of a very high *discordance* rate for congenital heart disease (see ¶ 168) and for cleft lip and palate (Douglas) in monozygotic twins is disturbing to the hypothesis advanced by Neel.

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115. Takala studied 241 families into which one or more malformed children had been born and an equal number with at least 2 normal children. The congenital malformations were as follows: 102 central nervous system, 15 blood or cardiovascular system, 46 alimentary tract, 6 genitourinary system, 55 extremities, 3 skin, 14 miscellaneous. The mothers of malformed children were 0.67 per cent of the obstetrical population of Takala's hospital in Finland. Of these, 8.7 per cent had more than one malformed child. In 52 per cent of the families with malformed children there were malformations in relatives. The abortion rate of mothers in the two groups was 9.4 ± 1.9 per cent for the malformation group and 6.8 ± 1.6 per cent for the control group. Alcoholism was increased in the malformation group but mental defect, suicide, epilepsy, and stillbirths had the same frequency. Of the families with more than one malformed member, 25.5 per cent had identical defects and 46.5 per cent had the same system involved. Acute infection (equally divided between bacterial and viral) occurred in 19.0 ± 2.5 per cent of all mothers of malformed children, in 25.5 ± 2.8 per cent of those with central nervous system malformation. There was no difference in the frequency of chronic diseases, operations, trauma, mental disease, x-ray, drugs, or poisons. The blood group combinations were significantly different in the parents of the malformation group.

116. Hill and co-workers concluded that maternal rubella in early pregnancy continues to be a significant cause of congenital malformations. In a prospective study, the incidence of congenital malformations in the offspring was 6 in 12 women (50 per cent) affected in the first month, 5 in 20 (25 per cent) affected in the second month, and 3 in 18 (17 per cent) affected in the third month. Although the numbers were small, mumps, chickenpox, and measles seemed to be exonerated.

117. Edwards found suggestions of marked environmental influences in the incidence of congenital malformations of the central nervous system (anen-

cephaly, spina bifida, hydrocephalus). There was marked association with social class. He suggested that it is not necessary to advance a genetic hypothesis to explain familial concentration of cases.

118. Congenital absence of the spleen appears to be almost invariably associated with severe cardiac malformation (Gilbert and associates). Although there is no evidence of a genetic basis, the syndrome is of great theoretical interest in teratology. An insult at the age of 24 to 28 days of the developing embryo appears to be responsible. Common mesentery and various degrees of malrotation of the bowel are frequent. The heart may consist of a single atrium, single ventricle, and truncus arteriosus. The theory was expressed that abortive ovulation or a hormonal by-product thereof, occurring at the time of the first ovulation after conception, might be responsible in some way for the abnormality observed in the 24- to 28-day-old embryo.

119. J. McKenzie provided a survey of what he terms "the first arch syndrome." In one category he would "lump" eight malformations previously considered separate entities: (1) Treacher Collins' mandibulofacial dysostosis (Franceschetti and Klein [1949] studied this form); (2) Pierre Robin's hypoplasia of the mandible with glossoptosis; (3) mandibular dysostosis; (4) deformity of the external and middle ear; (5) congenital deaf-mutism; (6) cleft lip and cleft palate; (7) hypertelorism; and (8) Waardenburg's broad nose root, lateral displacement of the inner canthi, white forelock, and congenital deafness. Although most would not agree with his conclusion that all these have a common genetic basis, it is useful to have it pointed out that the first arch area is particularly vulnerable to genetic and environmental causes of abnormal development. The group could well be considered together in any investigation of abnormal embryogenesis.

Metrakos, Metrakos, and Baxter reviewed 108 twin pairs, at least one of whom had cleft lip or cleft palate. Ten pairs were studied personally by these workers and the others were found in the literature. In monozygotic twins the concordance was found to be 31 per cent whereas of the dizygotic twins 6.3 per cent were concordant for the malformation—a figure not much higher than that for risk of recurrence in sibs of probands. The cases from the literature suffer from the possible bias of greater likelihood of report when both twins were affected. In one twin pair, discordant for cleft lip, monozygosity was proved by reciprocal skin grafting.

VIII. ALIMENTARY TRACT, INCLUDING SALIVARY GLANDS, PANCREAS, AND LIVER

The Pre-Stomach Tract.—

120. Keratosis palmaris et plantaris (tylosis) is, as far as the skin is concerned, a harmless hereditary state with heterozygous expression. The palms and soles show striking thickening of the skin. In two large kindreds studied by Howel-Evans, McConnell, Clarke, and Sheppard about 70 per cent of those with tylosis died of carcinoma of the esophagus. There is no evidence for an

important genetic factor in esophageal cancer independent of tylosis. Tylosis is probably not a single genetic entity. There is also a phenotypic heterogeneity. In type A the onset is between 5 and 15 years and carcinoma of the esophagus may be associated; in type B the onset is in the first year of life, the lesions are more sharply delimited, painful fissuring is rare, and carcinoma does not occur.

Stomach.—

121. Graham and Lilienfeld provided an appraisal of genetic studies of *gastric cancer* in man. Twin studies and studies of familial aggregation (both pedigree analyses and statistical studies) are available. They concluded that despite limitations of all studies to date the results indicate a concentration of cases of gastric cancer in certain families. How much of the aggregation is the result of genetic factors and how much environmental is difficult to say. "It will be most useful to compare the risk of gastric cancer among monozygotic and dizygotic twins that are selected at random from the population. . . . Of equal importance is . . . carrying out epidemiological studies of possible environmental determinants of the disease."

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See ¶ 86 with reference to pyloric stenosis.

Small Intestine.—

122. Wallace and associates found a significant excess of nonsecretor individuals among patients with *duodenal ulcer.* The hypothesis is advanced that mucopolysaccharides which contain the blood group substances have a protective action on the mucosa of the gastrointestinal tract and that the association of blood group O with duodenal ulcer may have its basis in such a mechanism.

123. A gliadin tolerance test was used by Payne and Jenkinson to diagnose *celiac disease.* An abnormal increase of apparent plasma glutamine was observed in affected children regardless of stage of disease or recovery.

According to Hyatt, tropical or nontropical sprue, childhood and adult celiac disease, and idiopathic steatorrhea (constituting what might be called the *primary malabsorption syndrome*) "are believed to be clinical variants of the same genetically transmitted metabolic derangement." However, an intensive clinicogenetic study has apparently not been performed.

A diet free of the proteins of wheat, rye, and oats has been found effective in the treatment of celiac disease. Sleisenger and colleagues found that it was also effective in 20 cases of nontropical sprue. The patients ranged in age from 22 to 67 years. The identity of the two conditions is suggested by this observation and also by the fact that 5 of the 20 patients had had celiac disease as children. Furthermore, 2 of the patients had a relative with celiac disease. The authors suggested that the basic pathogenetic mechanism may be the absence or deficiency of an intestinal enzyme, possibly a peptidase. Objective gauges of response to therapy included fall in fecal fat excretion, fall in urinary 5-hydroxyindole-acetic acid excretion, improvement in the x-ray appearance of the barium-filled intestine, and reduction in the cellular infiltration of jejunal mucosa obtained by suction biopsy.

124. Boggs described siblings with absence of the Auerbach ganglia and nerves from all bowel between the ligament of Treitz and the anus.

125. The report in 1949 by Jeghers and collaborators of a syndrome of generalized intestinal polyposis and melanin spots of the buccal mucosa, lips, and digits appears to have stimulated great interest and sharpened observations. The name *Peutz-Jeghers syndrome* has attained general usage. Guisto and associates were able to find at least 39 reports of the syndrome between 1949 and 1958; in 1958 at least 6 more reports appeared (Beinfield; Dormandy; Rintala; Bartholomew; Guillard; Dortenmann).

Bartholomew and Dahlin described 6 new cases of the Peutz-Jeghers syndrome and produced an interesting motion picture on the disease. In one patient, an 82-year-old man who died of coronary artery disease, one polyp in the stomach and 6 in the colon, all benign, were associated with characteristic melanin spots of the lips. The authors found 117 cases reported in the literature. About 55 per cent have more than one affected family member. The authors conclude the polyps are a developmental abnormality of the nature of hamartomas and not neoplasms. The evidence for this conclusion is (1) the low incidence of malignancy and (2) the presence in the polyps of smooth muscle, gastric secretory cells, cells of Paneth, and other elements normally found in the gastrointestinal tract.

Guillard and others reported upon an instructive family with affected persons in three generations. Interestingly 2 had polyps without spots, 2 had both polyps and spots, and one had only spots. Carcinomatous degeneration of the polyps must be very rare in this syndrome. It is not certain that a single case of metastatic carcinoma of this origin has been reported. Guillard's demonstration of relatively low DNA content and "weak nuclear activity" in the polyps may be relevant. Guillard's family seemed to demonstrate the phenomenon of anticipation. One of the affected persons had a pigmented spot on the cornea!

Large Intestine.—

126. Smith presented an interesting study of what he chose to call *Gardner's syndrome* for its original discoverer, E. J. Gardner (1951, 1952, 1953): multiple polyposis of the colon with epidermoid cysts and a proliferative tendency of mesenchymal cells leading to osteomas, fibromas, or desmoids. The presence of the epidermoid cysts on the face and extremities was particularly characteristic and often led to a misdiagnosis of neurofibromatosis. The desmoid tumors might appear spontaneously and were particularly prone to develop in abdominal incisional scars. The mandible was a favorite site for osteomas but in the group of patients surveyed by Smith, many other bones were at times affected. The entity was judged to be due to a single autosomal dominant pleiotropic gene. In diagnostic usefulness and in interesting demonstration of pleiotropism (probably pseudopleiotropism) the mesenchymal tumors of the Gardner syndrome bear the same relation to polyposis of the colon that melanin spots bear to the generalized intestinal polyposis of the Peutz-Jeghers syndrome.

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127. In a large family with *multiple polyposis* studied in New Zealand, Veale suggested that the polyposis locus may be linked with the MN locus.

The relationship between single or a few polyps of the colon and colonic cancer has come in for close scrutiny (Spratt and associates; Cole and associates) with the startling conclusion that polyps per se are not precancerous. The conclusion is based on (1) the difference in distribution of polyps and cancer in the colon (cancer occurs more in the cecum and sigmoid; polyps are more evenly distributed), (2) the fact that the frequency of occurrence of adenomatous polyps in cancerous and noncancerous colons of persons over 50 years of age is the same, (3) the lack of identifiable residua of polyps in colonic cancers, and (4) the rarity of infiltrative histologic changes in polyps. Cole and colleagues found that in those patients who at colectomy for carcinoma were found to have associated polyps the incidence of either lymph-node involvement or local extension was less than in those without polyps and the 6-year survival was greater. They raised the question of whether the "polyp-former" may have greater resistance to invasion by cancer. These remarks on isolated polyps do not relate to familial polyposis in which the incidence of cancer is, of course, striking. Since the colonic mucosa in such cases may be carpeted with myriads of tightly packed polyps, it is difficult to say whether the malignancy arose in a polyp or in "normal" mucosa. It is clear, however, that cancer can develop in the rectum stump left after colectomy in such patients even if the rectum is kept clean of polyps by local excision.

Dukes points out that polyps are rarely present in infancy in cases of familial polyposis of the colon but usually develop in childhood or early adulthood. During this period members of polyposis-prone families should be examined every two or three years, or immediately if bowel symptoms develop. In persons over the age of 40, if no symptoms of polyposis have appeared and if sigmoidoscopy is negative, it can be concluded that genetic predisposition to the disease is not present.

128. Woolf found a higher frequency of *colonic cancer* in the relatives of probands with cancer of the colon than among relatives of controls. Furthermore, collecting all available information on these families with colon cancer he seems to have excluded the possibility that the increased incidence in these families was due to the presence of familial polyposis.

129. Houghton and Naish estimated the general incidence of *ulcerative colitis* in the Bristol, England, area at 0.85 per 1,000 and that of regional ileitis at 0.14 per 1,000. In seven families, however, a strikingly high incidence was observed. Some members of the same family had one disease and some the other. The authors postulated a common hereditary factor predisposing to one or the other disease.

130. Freysz and his colleagues observed *regional ileitis* in identical twins.

Pancreas.—

131. Schwachman and Kulczycki reported on a long-term study of 105 patients with *cystic fibrosis of the pancreas.* Forty-one were over 10 years of age

at the time of completion of the study. Kulczycki and Schwachman commented on the relatively high frequency of rectal prolapse and suggested that in any infant with unexplained rectal prolapse the stool trypsin test, chloride imprint test, sweat electrolyte concentration, or duodenal fluid enzyme assay should be done.

Misch and Holden reported a fatality from heat stroke in a 13-month-old boy in whom the Schwachman sweat test for fibrocystic disease of the pancreas was performed. In the test the patient is wrapped in a plastic bag up to the neck and covered with a blanket. Sweat is collected in a weighed square of gauze on the back. The test is safe if the original recommendations of Schwachman be followed. One should not extend the test over 90 minutes, apply external heat by hot-water bottles, or give the patient sedatives—all rules which were broken in the fatal case. Schwachman further recommends that the test should not be performed on undernourished infants, especially those with respiratory distress or fever.

Barbero and Chernick confirmed the observations of di Sant'Agnese (1956) that salivary gland function is abnormal. The volume of the saliva, as well as its sodium and chloride content, from the unstimulated glands of cystic fibrosis patients was increased, and an abnormally great further increase occurred when stimulation with methacholine was used. There was no difference in potassium content from the normal.

Blanc and others found a diffuse deposition of ceroid pigment in the smooth muscle of the intestinal tract. The changes were attributed to defective vitamin E absorption in cystic fibrosis of the pancreas. Changes in striated muscle were rare. Reemtsma and his colleagues studied the absorption of I^{131}-labeled fat and fatty acids in 10 cystic fibrosis cases. Absorption of both was abnormal. Although fat malabsorption would be expected from a deficit of pancreatic lipase, a defect in fatty acid absorption was a surprise and suggested to these workers that there is an intestinal defect as well as a pancreatic one. Two of the 10 cases had tryptic activity in the pancreatic juice. However, the defect in fatty acid absorption was about as marked as in the other 8 cases, although neutral fat was better absorbed.

Caldwell and McNamara described a 24-year-old patient with diabetes and pulmonary disease from fibrocystic disease of the pancreas. Symptoms of pulmonary disease had begun at age 16.

Other reports included those of Jenkins and of di Sant'Agnese.

Liver.—

132. Campbell and colleagues observed identical twin sisters and a third sibling with bleeding esophageal varices secondary to *polycystic liver.*

133. Sutnick and Dyke reviewed the subject of Gilbert's constitutional hyperbilirubinemia.

Beker and Read provided a useful tabulation of differentiating features of three *hereditary hyperbilirubinemias* which have eponymous designations.

THREE HEREDITARY HYPERBILIRUBINEMIAS

	DUBAN-JOHNSON	GILBERT	CRIGLER-NAJJAR
Inheritance	Dominant?	Prob. dominant	Recessive
Jaundice	Mild	Mild	Severe
Onset	Prob. at birth	Prob. at birth	At birth
Choluria	Usually	None	None
Hepatosplenomegaly	Sometimes	Never	Always
Health	Good	Good	Bad
Prognosis	Good	Good	Bad
Serum bile pigments	Slight increase (bilirubin glucuronide)	Slight increase (bilirubin)	Marked increase (bilirubin)
Flocculation tests	Often abnormal	Normal	Normal
BSP excretion	Often abnormal	Normal	Normal
Increased hemolysis	None	None	None
Cholecystogram	Sometimes "nonfunctioning"	Normal	?
Liver biopsy	Coarse, granular, brown pigment in normal liver cells	Normal	Bile thrombi in canaliculi; slight scarring

134. Cain and Donato, in an autopsy study, concluded that *gallstones* are three times as common in whites as in Negroes.

Foster and Knutson seem to have established that cholelithiasis, hiatus hernia, and diverticulosis coli (Saint's triad) occur together more frequently than is explicable by chance alone. They suggested "congenital structural weakness" as a factor in the association. On the other hand, Fedele and Sabatini think the association is merely coincidence.

IX. BLOOD AND HEMATOPOIETIC SYSTEM

A. Disturbances of the Clotting Mechanism (see also ¶'s 36 and 86).—

135. The excellent general review by Brinkhous and colleagues is recommended. See also Morawitz' *The Chemistry of Blood Coagulation.*

Westlin, Mills, and Owen provided a useful review of hemophilias A, B (Christmas disease), and C (plasma thromboplastin antecedent [PTA] deficiency). The last is inherited as an autosomal dominant. Appreciation of the different types of hemophilia date only from 1952. The survey of Didisheim and Lewis is even more comprehensive. They point out that nine hereditary defects of the clotting mechanism are now known:

1. Hemophilia A (AHF)
2. Hemophilia B (PTC)
3. Hemophilia C (PTA)
4. Hageman factor deficiency
5. Hypoprothrombinemia
6. Hypoproaccelerinemia (parahemophilia)
7. Factor VII (SPCA) deficiency
8. Stuart factor deficiency
9. Afibrinogenemia

The first three represent, respectively, about 73 per cent, 21 per cent, and 1 per cent of all cases of "hemophilia." Parahemophilia (hypoproaccelerinemia) has been reported in about 20 families. It occurs in both males and females.

The same group (Didisheim, Ferguson, and Lewis) suggested that one cannot consider hemophilia A and B to be completely recessive sex-linked traits since mild abnormality occurs in a significant number of the heterozygous female carriers. They studied 63 obligate carriers of hemophilia A and 14 obligate carriers of B. Abnormality of coagulation was demonstrable in 12.7 per cent of form A and 28.6 per cent of form B. Over half the carriers with demonstrable defect by test had had significant hemorrhagic symptoms. Among those with normal tests, 20 per cent had had hemorrhagic symptoms, usually of milder grade.

Hemophilia-like states in females were discussed by Quick and Hussey.

In 9 cases of hemophilia Barkhan found a low serum cholesterol with a normal proportion of cholesterol in the beta-lipoproteins. Whether this was due merely to ill health and poor dietary intake is not clear. The observations have pertinence with reference to the theories of atherosclerosis and the question of the relative incidence and severity of atherosclerosis in hemophiliac patients.

Blombäck, and Blombäck and Nilsson studied antihemophilic globulin and treated hemophilia A with human antihemophilic globulin.

Rosin, Moor-Jankowski, and Schneeberger estimated the reproductive fitness of males affected by hemophilia B and of female carriers in the large kindred in Tenna, Switzerland. The fitness of bleeders was estimated to be $f = 0.64$. The fitness of carrier females was estimated by three methods yielding values averaging about 1.22. The authors suggested that the selection against bleeders could be countered by the increased fertility of carrier females without invoking mutation as a mechanism. Hematologic and clinical aspects were reported by Huser and his colleagues and in a monograph by Moor-Jankowski and his colleagues.

McGovern and Steinberg described a 6-year-old female with mild deficiency of antihemophilic globulin and hemophilic manifestations. The maternal grandfather had mild hemophilia of classical type with which he had survived to the age of 67 years. The child was thought to be a female carrier—that is, the gene was thought to be incompletely recessive—rather than a homozygote. Within the general class of hemophilia A (classical hemophilia) there may be two genetic entities. In one the disease is somewhat milder in the affected males and it is more customary to be able to demonstrate abnormality in carrier females. Are the two types allelic?

Seibert, Margolius, and Ratnoff found hemophilia and parahemophilia in the same patient, the fourth reported case.

McIlvanie reported on 24 patients with prolonged bleeding time and normal clotting time, clot retraction, platelet count, and platelet morphology. Excessive bleeding with dental extractions was frequent. The cases were thought to fit von Willebrand's thrombopathic state. Multiple affected family members was the rule. In some families an autosomal dominant inheritance seemed likely. Adrenal steroids were beneficial. Horler and Witts also wrote on von Willebrand's disease and used the designation "hereditary capillary purpura."

Valberg and Brown reported on a large family with a defect in both the vascular and the coagulation mechanisms of hemostasis. It was transmitted as an autosomal dominant. Of interest was the fact that the great-great-grandfather was an Italian fisherman by the name of Alfredo Purpura! Evidence was presented that the coagulation defect represents a deficiency of antihemophilic globulin. Much remains to be determined about the genetics, relation to classical hemophilia, nature of the physiologic defect, and other aspects in the "vascular hemophilia" group which probably comprises several distinct entities.

B. Genetic Disorders of White Blood Cells.—

136. Payne and Rolfs studied fetomaternal *leukocyte incompatibility.* Leukoagglutinins were found in 25 of 144 multiparous women. Of these 7 had received intravenous or intramuscular injections of blood. The leukoagglutination test was considered positive when agglutination in two or more members of the leukocyte panel (leukocytes from 10 persons of red cell group O) occurred. Iso-leukoagglutinins of the maternal sera agglutinated the leukocytes of 10 of 12 of their respective newborn infants, and 12 of 13 of their respective spouses, thus suggesting the inheritance by the offspring of the father's leukocyte factor. Febrile transfusion reactions occur more frequently in multiparous women and can be avoided by administration of blood from which the majority of the donor leukocytes have been removed. Search for distinct leukocyte types has, thus far, been attended with limited success.

137. Undritz wrote on the *Chediak-Steinbrinck anomaly* of leukocytes. Described by Chediak of Cuba (1952) and Steinbrinck of Breslau (1948), the anomaly is characterized by giant granules which may occur in the plasma cells as well as the polymorphonuclear leukocytes, lymphocytes, and monocytes. It is inherited as an autosomal recessive. Most of the affected persons are albino and die at an early age from infections to which they are abnormally susceptible.

138. Undritz also described an interesting family with *hypersegmentation* of the nuclei of the polymorphonuclear leukocytes. The trait is expressed in the heterozygote. When 2 heterozygotes married, however, he observed one unaffected child, 3 children who were probably heterozygous, and one who may have been homozygous for the rare mutant since the degree of hypersegmentation was extreme. Barbier also found 3 individuals with hypersegmentation in three generations of a family. One patient developed hypersegmentation of lymphocytes, monocytes, and plasma cells during a bout of Henoch-Schoenlein purpura.

139. The *Pelger-Huët anomaly* of leukocytes (hyposegmentation) was studied by Redies and associates, by Hittmair and Leibetseder, and by Ciplea and Ciorapciu.

140. Hahneman and Alt described a 29-year-old man who from an early age had *cyclic neutropenia,* occurring every 21 days and accompanied by infec-

tions. Complete remission occurred at age 18. The man's daughter was seen at the age of 2 years with similar periodic disease recurring each 14 days. The familial aspect of periodic disease was reviewed. Torrioli-Riggio also reported on familial cyclic granulopenia.

141. Cramblett and colleagues observed acute lymphocytic *leukemia* in the newborn offspring of a mother also with acute lymphocytic leukemia. The authors mentioned the possible role of heredity or of a transmissible agent in this association. Santos raised the additional intriguing possibility that because of partial immunologic tolerance which an infant may develop in utero toward the mother's tissues a transplantation of leukemic cells to the mother may have occurred. He suggested that the hypothesis could have been tested by demonstration in the infant of maternal erythrocytes (by blood grouping) and maternal granulocytes (by looking for female nuclear sex in the male child) and by the acceptance of a maternal skin graft by the child.

Videbaek, who in 1947 reported on a study of the familial incidence of leukemia, described three families with multiple cases. He also commented on the association of Mongolism and leukemia.

C. Genetic Disorders of the Erythron.—

142. Lange and Akeroyd described a case of *congenital hemolytic anemia* with abnormal pigment metabolism and red cell inclusions. It may be a new syndrome. Although there were no other cases in the family and the parents' blood was normal, a genetic basis is possible. The inclusion bodies were distinctive from any inclusions previously described.

143. Gerald and Diamond described the diagnostic use of starch block electrophoresis for recognizing the *thalassemia* trait—by increase in the A_2 fraction of hemoglobin. Furthermore, two papers from the laboratory of the late Dr. Karl Singer described starch block electrophoresis of cord blood, and in thalassemia, and other situations (Masri; Josephson).

In a collaborative study from Rome and London, no evidence of linkage was found between thalassemia and the haptoglobins (Siniscalco and others).

Sickle cell–thalassemia, studied extensively in Italy by Silvestroni and Bianco, who called it microdrepanocytic disease, was the subject of several reports (Brown and Ober; Went and MacIver).

The pathogenesis of acute crises in *hereditary spherocytosis* is obscure. Some of the crises can be described as "aplastic" since anemia, thrombocytopenia, and reticulocytopenia are associated with erythroid hypoplasia of the marrow. Splenectomy was of doubtful benefit in the "aplastic" crises of a mother and son (Denny). Burman recommended that splenectomy be postponed until after the period of infancy since the risk of infection, often fatal, is great in splenectomized infants.

144. Gelpi and Ende studied 2 brothers, in their thirties, with what they interpreted to be the sex-linked or sex-influenced hereditary anemia described

originally by Cooley and later by Rundles and Falls. A sister and the mother displayed minor alterations in red cell morphology. A striking similarity of red cell morphology to that in thalassemia and evidence of a poorly compensated hemolytic process led to the authors' suggestion that this be called "pseudothalassemia." Hemochromatosis was a complicating feature.

145. Further cases of hemolytic anemia in association with *hereditary elliptocytosis* were reported, 3 in a Portuguese family (Ducla Soares and Parreira) and one in an English family (Blackburn). Mongan observed coexisting elliptocytosis and hemoglobin C trait. As in the cases of Avery (1956) the combination had no pathologic consequences.

146. Zweymüller and his colleagues described a 7-year-old child, with *Fanconi's anemia* (they term it "constitutional infantile panmyelopathy"), who in addition to pigmentary changes in the skin and renal malformation (frequent findings in this syndrome), had patent ductus arteriosus and hydromyelia.

147. Arbo and Mohr observed *pernicious anemia* in monovular twins. Fusco and Bouroncle observed pernicious anemia and sickle cell trait in the same patient.

148. Auerback, Wolff, and Mettier described two families with "benign familial *polycythemia*" in children, which they suggest is distinct from polycythemia rubra vera of adults. Two boys and a girl, from normal parents, were affected. In another family a girl with normal parents and 2 normal brothers had polycythemia as did also an aunt. There was no leukocytosis, thrombocytosis, or hyperuricemia; the spleen was slightly enlarged in 3. There were no symptoms and the course was apparently benign.

Pike, in reviewing the subject of polycythemia, pointed out that although the familial aggregation is recognized, the fundamental nature of the disturbance is unknown. The disease was found less commonly in Negroes (who tended also to have milder disease) and more commonly in Jews (Damon). No characteristic body build was discovered.

Hemoglobinopathies: 149. The genetic abnormalities of hemoglobin were very well covered in the Conference on Hemoglobin, Publication 557 of the National Academy of Sciences—National Research Council. (The conference was held May 2-3, 1957; the publication appeared in 1958.) The published proceedings are divided into five parts: (1) The structure of hemoglobin, (2) the biosynthesis of hemoglobin, (3) abnormal hemoglobins, (4) genetic aspects of abnormal hemoglobins, and (5) clinical characteristics associated with abnormal hemoglobins. The following is only a small sample: Kunkel (Rockefeller Institute) presented evidence for the presence of two minor hemoglobin fractions in normal blood. Hb A_2 is increased in thalassemia and, as far as is known, only in this disease. The second minor fraction is less clearly defined. Except for fetal hemoglobin Chernoff (Duke University) could demonstrate no immunologic

differences between several hemoglobins tested. Ingram (Cambridge University) presented the result of his combined electrophoresis-chromatography of hemoglobin which leads him to the conclusion that the difference between Hb A and Hb S resides in a single amino acid substitution in one of the amino acid sequences ("fourth peptide"):

			++									−	−	+−			
*Hb A	His	Val	Leu	Leu	Thr	Pro	Glu	Glu	Lys								
			++										−	+−			
Hb S	His	Val	Leu	Leu	Thr	Pro	Val	Glu	Lys								
			++								+	+−	+−				
Hb C	His	Val	Leu	Leu	Thr	Pro	Lys	Glu	Lys								

These observations open up new vistas on how genes work. They provide support—if any is required—for the view that S and C are allelic (Hunt and Ingram).

Neel (University of Michigan) pointed out that three alternative explanations for the advantage of the sickle heterozygote with reference to malaria have been suggested: (1) The *falciparum* parasite may have more difficulty metabolizing Hb S. (2) The presence of the malaria parasite in the red cell may precipitate sickling by reducing oxygen tension. The sickled cells together with the parasite may then be removed from the circulation. (3) Because of factor 2 the placenta may be less severely affected by malaria in the sickle heterozygote.

Neel also reviewed the information on the genetics of the hemoglobinopathies. Hemoglobins A, S, and C appear, from the pedigree data, to be determined by allelic genes, and this conclusion is, of course, nicely corroborated by Ingram's information. Hemoglobin G is controlled by a different locus and thalassemia by yet another. Neel discussed the probable genetic (and clinical) heterogeneity of thalassemia.

Smith and Conley (Johns Hopkins University) described the instructive case of an 11-year-old Negro male with the combination of sickle cell trait and tetralogy of Fallot. Because of severe reduction in arterial oxygen saturation (to 64 per cent) the hematologic picture was that of sickle cell anemia. After Blalock subclavian-pulmonary anastomosis the anemia disappeared. They pointed out that sickle–hemoglobin C disease presents features which neither sickle cell disease or hemoglobin C disease in pure form shows. Peculiar aneurysms, twisted vascular loops, and fine networks of vessels are essentially unique to HbS-HbC disease.

Many other aspects of the hemoglobinopathies were discussed in this important symposium.

Other publications on hemoglobin variants: 150. Hemoglobin C. Three patients with homozygous hemoglobin C disease in Negro women aged 28, 32, and 67 years, had hepatosplenomegaly and mild hemolytic anemia without sickling (Tanaka). (See also Hook and Cooper.)

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*More recent work has required revision in the diagramming of the sequence at the left hand end of the scheme.

151. Hemoglobin D. Chernoff discussed the hemoglobin D syndromes. The trait (heterozygous state) produces no clinical or hematologic abnormality, while the homozygote described by Chernoff had mild microcytic normochromic anemia with decreased osmotic fragility and slight shortening of red cell survival.

152. Hemoglobin E. Brumpt and his colleagues found a high incidence (35 per cent) of hemoglobin E among Cambodians (Siamese).

153. Hemoglobin H. Bingle and associates found hemoglobin H disease in two families with no thalassemia. Hemoglobin H disease closely resembles thalassemia minor. Previously hemoglobin H disease has been described only in ethnic groups commonly affected by thalassemia. This had led to the hypothesis that there is an interaction between the H gene and the thalassemia gene. Bingle's observation seems to disprove this hypothesis.

Wolff and co-workers described a single case of an Italian child with a mild form of Cooley's anemia on the basis of hemoglobin H–thalassemia disease ("inclusion body anemia"). Hedenberg described "hemoglobin H and inclusion-body anemia in a Swedish family."

In a 24-year-old Chinese seen in Singapore, Vella, Ager, and Lehmann found chronic hemolytic anemia due to a combination of hemoglobin H and a new hemoglobin the authors called hemoglobin Q, since at the time of the report other letters of the alphabet up to Q (except, of course, B which has not been used) had been taken.

154. Hemoglobin M. In his report on the electrophoretic and spectroscopic characteristics of Hb M, the basis for some cases of methemoglobinemia, Gerald pointed out that this was the first described abnormal hemoglobin; in 1948 Hörlein and Weber demonstrated an abnormality of the globin part of the hemoglobin molecule. The pedigree pattern suggests dominant inheritance.

Heck and Wolf described cyanosis due to hemoglobin M in a 5-year-old boy. As in many such cases congenital heart disease was first diagnosed; in this case pulmonary stenosis was in fact found to be present but could not account for the cyanosis. The abnormal pigment caused a change in light absorption at 600 mμ. Since typical methemoglobin does not have this absorption characteristic and since the response to methylene blue and vitamin C was equivocal, the defect was thought to reside in the globin part of hemoglobin.

155. Hemoglobin S. The gravity of the obstetrical problem in patients with sickle–hemoglobin C disease was emphasized by Eastman. Of 6 pregnant Negro women with this disease seen in a 5-year period at The Johns Hopkins Hospital 3 died in pregnancy or labor (2 from postpartum hemorrhage, one from bone marrow emboli). Shelley and Curtis also reported on bone marrow embolism.

Levin's editorial reviewed the mild and occasional symptoms of sickle cell trait—not insignificant manifestations since they can potentially occur in about 8 per cent of the Negro population of the United States (some 1½ million per-

sons) and in millions more in Africa. Hematuria, infarcts and rupture of the spleen, hemolytic disease with heart failure, and pulmonary and cerebral thrombi are among the manifestations attributed to sickle cell trait. The possibility exists that any condition producing hypoxia, local or systemic, will induce intravascular sickling and contribute to the pathologic picture.

Among the Gullah Negroes of South Carolina, Pollitzer found as high an incidence of abnormal hemoglobins as in parts of West Africa and compared hemoglobins, blood groups, and other data with those from West Africans and other Americans, white and Negro. He suggested that the persistence of a high S frequency may be because malaria remained endemic in the Gullah region until very recently. MacIver, Went, and Cruickshank, and Went and MacIver found sickle cell anemia, sickle-thalassemia, and other hemoglobinopathies in Jamaica.

Studies of cardiopulmonary function in sickle cell anemia (Sproule, Halden, and Miller) suggested that arterial oxygen unsaturation is due to venous admixture in the lung, that pulmonary vascular resistance is often reduced, and that cor pulmonale is probably much rarer han has been thought.

156. Smith and Torbert at Johns Hopkins described two new "fast" hemoglobins and temporarily designated them "Hopkins 1" and "Hopkins 2." An interesting aspect was description of a new "hemoglobin locus." In one family offspring derived sickle hemoglobin and Hopkins 2 hemoglobin from the same parent indicating that the genes responsible are not allelic.

Ager and his associates also found an apparently new hemoglobin which at pH 8.6 migrates slightly faster than both A and J. It is the first abnormal hemoglobin, according to the authors, found in an English family (from Norfolk). Following a suggestion by Neel's group that initially hemoglobins be named for the place of discovery, the workers tentatively called it hemoglobin Norfolk. The problems associated with hemoglobin nomenclature were discussed and a grouping of adult hemoglobins into 6 categories according to mobility on paper at pH 8.6 was proposed.

No abnormal hemoglobins were found by paper electrophoresis in 397 Oriental Jews, although thalassemia is not rare and the primaquine-sensitive erythrocyte defect occurs rather commonly (Dreyfus and Pinkhas).

D. Blood Groups (see also ¶'s 1, 13, 15, 19).—

157. Manuila expresses the opinion that too little attention has been paid to the ethnic composition of the population studied when associations between specific blood types and specific diseases have been claimed. However, that stratification cannot be the explanation for some of the reported associations, particularly peptic ulcer and blood type O, is indicated by the fact that it has been described in many parts of the world and in many different ethnic groups. Buckwalter and Knowler examined the question of what the proper controls are for such studies.

Mosbech found increased frequency of blood group A in a group of 1,764 patients with stomach cancer. He could find no difference according to location in the stomach, contrary to the findings of Billington. Helmbold and associates found an increased frequency in a group of patients with carcinoma of the cervix.

158. Making a comparison to the "dumpy" locus of *Drosophila melanogaster*, Carlson proposed a genetic interpretation of the Rh blood group series which is different from either the multiple allele hypothesis of Wiener or the closely linked gene hypothesis of Fisher and Race. The dumpy locus has been found to have at least seven mutable sites separable by crossing-over. The complex locus occupies only about 0.13 map units and adjacent mutable sites have recombination frequencies of the order of 0.01-0.04 per cent. According to Carlson's pseudoallele theory of Rh, each allele represents a mutation at a different site within the Rh region.

Wiener again stated his position on the subject of blood group nomenclature.

159. Reilly and colleagues observed transfusion reactions in an individual with anti-M sensitization, when M-positive blood was given and not when M-negative blood was given. The circumstances of the case suggested that the isoantibody was of natural origin.

The Diego blood group factor, rare in Caucasians, frequent in American Indians, was studied in Peruvian Indians by Allen. Relation to several of the other blood group systems has been excluded. It may, however, be related to one of the well-studied systems such as the Kell group.

160. Using as a marker the blood of sickle cell trait persons and transfusing this into pregnant women just before delivery, Macris, Hellman, and Watson demonstrated that maternal red cells can pass into the fetus. Because of the pressure relationships in the several vascular compartments of the placenta it has hitherto been thought that exchange occurs only in the opposite direction—from fetus to mother. The mechanism of the maternofetal exchange is not clear. This finding has interesting implications with reference to immune tolerance.

161. Clarke and colleagues, in a family study, further corroborated the protection afforded by ABO incompatibility against erythroblastosis due to Rhesus anti-D. Leikin, Rheingold, and Sites discovered evidence of ABO erythroblastosis in 5.6 per cent of 230 mother-infant pairs with ABO incompatibility. The total number of mother-offspring pairs surveyed was 1,125.

162. Atwood made the important observation of the presence of some A_2 erythrocytes in A_1 blood. He proposed two alternative explanations: (1) somatic mutation might account for the finding; (2) the A_2 cell might be phenocopies ("serological freaks").

163. Unusual red cell antigens and antibodies were described by Huestis and Bates, Glover and Walford, and others. Neimann-Sørensen discussed blood groups in animals.

Mohn and colleagues studied the relationship of the blood group antigens Mi^a and Vw to the MNSs system. The first of these antigens was discovered by Levine and others (1951); the second by van der Hart and associates (1954). Both antigens were identified through antibodies produced in a mother in response to immunization by an incompatible fetus. This investigation demonstrated that the genes Vw and Mi^a are part of the MNSs complex of genes. In white people Vw showed a preference for travelling on an Ns chromosome, whereas Mi^a tended to travel on an MS chromosome. Vw and Mi^a are not alleles of M or N, or S or s. It could not be determined—and will be difficult to determine—whether they are allelic for other rare components of the MNSs complex (Hu, He, or Vr).

E. Others.—

164. Herrell and associates found multiple myeloma in brothers aged 53 and 55 years. This may represent coincidence since no similar instances could be found reported in the literature or among some 550 patients with multiple myeloma seen at the Mayo Clinic.

165. Crone and Bergin described Gaucher's disease in identical twins.

X. CARDIOVASCULAR SYSTEM

A. Hypertension.—

166. Fraser Roberts, who with Pickering and colleagues had pointed out that blood pressure level in the population is a continuous variable, published a plot with logarithmic abscissa, pointing out that the positive skewness disappears. He also reanalyzed data of Barnes and Browne on blood pressure in first-degree relatives of patients with toxemia of pregnancy; using his scoring device to remove the effects of age and sex, he concluded that blood pressure is higher in such relatives than in the population at large.

In connection with a consideration of environmental factors Miall and Oldham reviewed their data pertinent to the inheritance of arterial pressure. The over-all regression of all first-degree relatives on all propositi had a value of 0.224 (S.E. ± 0.022) for systolic pressure and 0.178 (S.E. ± 0.024) for diastolic pressure. Correction for arm girth enhanced the correlation. The separate regressions for relationships involving female propositi showed some heterogeneity which warrants further investigation. The data of this study were derived from 612 families of propositi ranging in age from 5 to 80 years.

With regard to racial difference in blood pressure Perry pointed out the difficulties in evaluating blood pressure in the native African because of anemia, parasitic and other infections, and malnutrition. Sankale and associates stated that hypertension and its complications occur frequently in the native African, although more rarely in the poorer, rural classes than in the urbanized, sedentary gourmand. Neel was impressed with the frequency of hypertension in the wards

for "acculturated" Negroes (e.g., government workers) in West Africa as compared with the ward for primitive natives. He suggested that white populations have already made some biological adjustments to the hypertensive influences in our modern culture but the Negro has only more recently become exposed. (See ¶ 70.)

Hyperreactivity to the cold pressor test, a trait which from twin and family data has been thought to be genetically determined, was found to be poorly predictive of subsequent hypertension (Harlan), contrary to previous conclusions.

Kincaid-Smith, McMichael, and Murphy could find no higher incidence of a positive family history in cases of the malignant (or accelerated) phase of essential hypertension than in cases of malignant hypertension due to assignable cause such as chronic glomerulonephritis. This finding is also contradictory to earlier ones.

Dahl recommended that dietary sodium chloride should not exceed 5 Gm. in any person and pointed out that under ordinary environmental circumstances this is an amount 10 times that necessary to maintain adequate balance. "For persons with a family history of hypertension, I should recommend the early adoption of a diet frankly low in salt—namely, levels of 500 to 1,000 mg. per day at the maximum."

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B. Atherosclerosis, Including Coronary Artery Disease.—

167. Russek and Zohman found a "positive family history" (cardiovascular disease in one or both parents) in 67 of 100 persons aged 24 to 40 years with coronary artery disease and in 40 of 100 persons in the same age group without clinical evidence of coronary artery disease. In only 16 of the "coronary group" were both parents living and well, whereas the corresponding figure for the control group was 40. Benedict described identical twin sisters with coronary artery disease; they had no diabetes or hypertension and serum lipids were only in the upper limits of what was interpreted as the normal range. Harvald and Hauge in a preliminary report of early results from a large twin study in Denmark could find no evidence for a genetic factor in coronary artery disease. Further results will be awaited with interest.

Vecchi and his associates found an excess of endomorphs and mesomorphs in a series of cases of coronary artery disease. Gertler, White, and colleagues (1954) also found a deficiency of ectomorphs.

Genetic differences in clotting propensity constitute a possible mechanism for familial aggregation for coronary artery disease. Mustard found that men with clinical complications of atherosclerosis or with such a family history showed greater enhancement of clotting activity (as measured by increase in Christmas-factor activity and decrease in antihemophilic globulin activity) after a meal of dairy fat and eggs than did controls. Studies of hypercoagulability, as opposed to those of hypocoagulability, are relatively new. In a review of the subject of the influence of dietary fat on blood coagulation Hashim and Clancy found most agreement regarding the accelerating effect of fat on the so-called Stypven time.

Genetic determination of coronary artery arborization, of intercoronary anastomoses, and of variations in the walls, e.g., in intimal thickness, are difficult to establish in man. Precedence is provided by other vascular patterns of man known to be genetically influenced: the antecubital venous pattern, the vascular pattern of the anterior thorax, aortic arch branching. Studies in animals (Vastesaeger and co-workers, 1957) and in man (Laurie and Brown; Laurie and Woods) suggest that the extent of intercoronary anastomoses is a congenital feature and not a response to demand later in life. Laurie and Brown found a high incidence of well-developed anastomoses in the South African Bantu and suggested that these may account in part for the relative protection against ischemic heart disease (Schrire).

Maher and colleagues described the clinical history and autopsy findings in 2 patients with essential hypercholesterolemia and coronary heart disease. The patients died at 13 and 17 years of age. Calcific aortic stenosis was present in both. The presence of foam cells in lymph nodes, mural endocardium, and pulmonary artery as well as the extravascular deposits suggested to the authors a distinction from ordinary "idiopathic" atherosclerosis. The possibility that the difference is only a quantitative one remains. Proper stains revealed metachromasia in the media of the arteries, apparently in relation to degeneration of elastic fibers.

If one grants that a disturbance in lipid metabolism, expressed by elevation of blood lipids, predisposes to atherosclerosis, one can take the sizable body of evidence on the genetic control of lipid metabolism as evidence for the genetic influence in atherosclerosis. Probably mainly because of relative ease of chemical determination, serum cholesterol has been the most frequently employed index of lipid metabolism. Studies in twins, monozygotic and dizygotic, living together and living apart, indicate that both genetic and environmental factors are operative in determining the level of serum cholesterol (Osborne and Adlersberg).

Schaefer, Adlersberg, and Steinberg reported on the intrafamilial correlations for serum cholesterol level. Whereas the parents showed no correlation, the parent-child and sibling-sibling correlations were significantly different from zero. A similar study of serum phospholipids was also conducted by the same workers, in 156 families. Serum phospholipid level showed an age trend which was different in the two sexes and which was similar to, but of lesser magnitude than, the age trend of serum cholesterol level. The correlation between the serum phospholipid levels of mothers and fathers was essentially zero while that between fathers and their children and mothers and their children were each significantly different from zero.

Although the incidence of acute myocardial infarction was found to be 2.2 times greater in the whites of North Carolina than in the Negroes, Weissler and collaborators could find no difference in the degree of duration of alimentary lipemia after a standard fat meal.

The data on serum cholesterol and other lipids would suggest that the etiology of coronary artery disease in young patients is more closely related to lipid disturbances than it is in older patients (Oliver).

Goldenberg and Blumenthal studied the relationship between diabetes mellitus and atherosclerosis. An increased frequency not only of myocardial infarction but also of hypertension was found in diabetic patients. In those without hypertension there was no significant difference between diabetics and nondiabetics in the incidence of myocardial infarction.

Robinson and colleagues observed two brothers with the Leriche syndrome (thrombotic obliteration of the bifurcation of the aorta). Two brothers have been operated on at The Johns Hopkins Hospital, for the Leriche syndrome.

C. Congenital Malformations of the Heart and Great Vessels.—

168. Siller provided evidence for a genetic basis for ventricular septal defect in the domestic fowl. In three inbred strains of Brown Leghorns, the incidence was 84.2 per cent, 49.5 per cent, and 31.4 per cent, respectively. The genetic behavior suggests a polygenic mechanism.

In man, a slight degree of familial aggregation for the commoner varieties of congenital heart disease has been found by several studies. There has been disagreement as to the degree of intrafamilial similarity in type of malformation. Miller and Zervopoulos concluded that if malformations are divided into "early" and "late" categories, there are close intrafamilial similarities. Their "early" category included transposition of the great vessels, tetralogy of Fallot, and truncus arteriosus—malformations dating from the time of rotation and involution of the bulbus arteriosus. Their "late" category included patent ductus arteriosus, coarctation, and atrial septal defect.

The high frequency with which monozygotic twins display *discordance* for congenital heart disease was again emphasized (Yuceoglu; Jones).

Examples of extraordinary families with multiple cases of congenital heart disease continue to be reported. Weinstein reported atrial septal defect in more than one member of families and in more than one generation. Carleton and colleagues reported upon three families in which a total of 9 cases of congenital heart disease was observed. In 3 members of one family (sibs) there was atrial septal defect. In another family ASD occurred in parent and child. The authors propose a simple autosomal recessive inheritance. This conclusion was based on the close approximation to a 1:3 ratio observed in 3 sibships which had in toto 30 siblings with 7 affected. Metrakos (New England J. Med. 260:562, 1959) pointed out that in calculating the risks of other relatives such as sibs being affected all sibships observed must be included. Furthermore, Metrakos estimated, on the basis of Carleton's statement that there were 37 other consecutively observed sibships in which only the proband was affected, that the incidence of congenital heart disease in sibs of congenital heart disease probands is about 2.72 per cent—a figure consistent with that obtained by others, e.g., Lamy and associates (1957). The problem here is the familiar one in the medical literature: a few families which show striking familial aggregation are picked out of many. If the condition under study shows a modest familial aggregation one must expect occasional families with striking pedigrees. The possibility often remains that the disease under discussion is heterogeneous and that there is indeed a uni-

factorial form of the disease in some families. (See Stephens and co-workers, ¶219, for a similar discussion.)

Although the sex ratio for all cardiovascular malformations approaches unity, pronounced deviations occur for individual entities (Keith, Rowe, and Vlad). There is an excess of males affected by tetralogy of Fallot, coarctation, transposition of the great vessels, and aortic stenosis. There is an excess of females with patent ductus arteriosus and atrial septal defect. The basis of these deviations is unknown.

169. In the *Ellis-van Creveld syndrome* congenital malformation of the heart, most often single atrium, is associated with chondrodystrophy, polydactylism, and hypoplasia of the nails and teeth (Smith and Hand; Mitchell and Waddell). It is inherited as an autosomal recessive. In contrast to classical achondroplasia, the root (proximal) bones of the extremities are, relatively speaking, the longest. Fusion of the capitate and hamate bones is pathognomonic.

170. Overholt and Bauman described sibships in which some members had the full *Kartagener syndrome* (situs inversus viscerum, bronchiectasis, and hypoplasia of the paranasal sinuses) whereas others had all the features except situs inversus viscerum. Other cases were reported (Misra). Brandt and Revaz found situs inversus viscerum in one of monozygotic twins.

171. Eliot and colleagues reported for the first time on endocardial fibroelastosis in cats and dogs. The disease is apparently identical clinically and pathologically with that in man and leads to death from heart failure in early life. In man the occurrence of endocardial fibroelastosis in identical twins and in sibs suggests a genetic factor in its etiology (Rosahn, 1955). In some of the litter mates of the kitten studied by Eliot the disease probably also occurred because an identical clinical course was followed; unfortunately all but one of the litter were destroyed and the mother was spayed because the breeder concluded she carried a hereditary disease. "Partial aortic stenosis" was also present in both the cat and the dog described by Eliot.

172. Lewis and associates described deaf-mutism and pulmonic stenosis in several members of a Negro family; the mother and 3 of 5 children had pulmonic stenosis. Two of the children affected with pulmonic stenosis also had deaf-mutism. The association was probably coincidental.

173. Another syndrome with deaf-mutism and cardiac manifestations was reported by Levine and Woodworth: congenital deaf-mutism, prolonged Q-T interval of the electrocardiogram, syncopal attacks, and sudden death. A single biochemical defect to account for all aspects was postulated. Familial incidence had been established by other observers.

D. Miscellaneous Cardiovascular Conditions.—

174. Arnoldi collected the histories of families with multiple cases of venous insufficiency (varicose veins) in the legs. In 100 cases of leg ulcers of unspecified

type, a family history of varicosities was present in 100. Arnoldi thinks that late menarche is a contributing factor in varicosities, or in some way related.

175. The pathogenesis of Buerger's thromboangiitis obliterans has been a matter of uncertainty (Gore). Whether it is an entity fundamentally distinct from atherosclerosis is the issue at question. Genetic and epidemiologic studies, together with studies of blood lipids, might help settle the question.

176. In one kindred reported by Hagy and Danhof, Milroy's hereditary edema and hereditary angioneurotic edema were passed through four generations but the diseases were in different lines of the family. One individual inherited the first condition from his father and the second from his mother. There seemed to be no interaction of the genes when present in the same individual. The Milroy's disease was of the late form, displaying onset from the age of 11 to 42 years. A mean value of 2.8 Gm. per 100 ml. was found for the protein of edema fluid in 38 cases of primary lymphedema (Taylor).

177. Several reports of hereditary hemorrhagic telangiectasia (Osler-Rendu-Weber syndrome) appeared (Mortensen). There were also reports of of pulmonary arteriovenous fistulas (Fletcher and associates; Steinberg and Miscall) which often occur in the Osler-Rendu-Weber syndrome.

XI. THE CONNECTIVE TISSUE SYSTEM

(*See also Section XIX, The Skeleton.*)

A. Genetically Determined Disorders.—

178. Clinical features of the *Marfan syndrome* were described in several reports (van Buchem; Marks; Sinha; Watzke; McKusick; Gonin and others; Jouve and others). Sinclair emphasized the musculoskeletal features which might lead the patient to the rheumatologist. Attempts to repair the ascending aorta have been unsuccessful (Fay) although the descending thoracic aorta has been replaced by a graft in a case in which it was predominantly involved (Baker). Pregnancy, which increases the risk of dissecting aneurysm in women without the Marfan syndrome, also increases the risk in women so affected (Husebye). Hirst and colleagues reviewed reports of multiple cases of dissecting aneurysm in families; many of these, as they pointed out, are cases of the Marfan syndrome.

Attempts at estimation of gene frequency or of mutation rate are beset by difficulties such as diagnostic doubts and difficulty of ascertainment in mild cases, variability in age at onset of some manifestations, especially the aortic ones, and the mimicry of phenocopies. The same difficulties attend the study of other dominant traits such as dystrophia myotonica. Lynas estimated the phenotype frequency to be not less than 1.459 per 100,000 and the mutation rate to be about 5 per million genes per generation. She could not demonstrate genetic linkage with sex, color vision, phenylthiocarbamide tasting, and seven blood group systems.

Bacchus found diminished serum mucoprotein in the affected members of a single family. Sjoerdsma and colleagues found, in some cases, an increase in the urinary excretion of hydroxyprotein, an amino acid unique to collagen.

179. Osteogenesis imperfecta. Caniggia and colleagues produced a monograph reviewing all aspects of the disease and based on four families in which 23 of 113 persons suffered from the disease. They conclude the disease is a monogenic, dominant, autosomal trait. Chromatography of the urine showed no abnormal aminoaciduria. They think estrogen in females and androgen in males reduce the incidence of fractures but find it difficult to obtain objective evidence in support of this impression. Coop reported on the disease in cats and the beneficial effects of sex hormones in affected animals.

Kostinen observed an 8-year-old boy in whom blue sclerae, scanty subcutaneous tissue, loose-jointedness, and scoliosis, in addition to fragilitas ossium, make the diagnosis of OI likely although no other cases occurred in the family. The feature of note was the development, in one femur, of massive hyperplastic callus formation simulating osteogenic sarcoma. In fact, interileoabdominal amputation was performed, on the basis of a mistaken diagnosis. Subsequently a similar hyperplastic callus developed in the opposite femur. For a prolonged period the patient was slightly febrile and had elevated sedimentation rate and alkaline phosphatase.

180. In *pseudoxanthoma elasticum*, studies of the tissues led Rodnan and colleagues, Fisher and colleagues, and Warren and colleagues (all from Pittsburgh) to the conclusion that the elastic fiber is the faulty element of connective tissue—the original view of Unna. In recent years the disease has tended to be viewed as a form of "elastotic degeneration of collagen." Although the matter cannot be considered settled, the evidence for elastic fiber abnormality is increasing. It may be that the uncertainty of the location of the basic defect is merely an expression of the intimate interrelationship of elastin and collagen. The observations by the Leeds group (Keech) on the transformation of collagen to "elastin" is consistent with a close relationship.

Further descriptions of the clinical behavior and the histopathology in visceral vessels (Woo and Chandler; Nellen; Edwards) appeared.

181. In *the Hurler syndrome* (gargoylism), the discovery that relatively large amounts of mucopolysaccharides are excreted in the urine (Meyer; Dorfman) has provided not only a means of differentiating it from entities such as the Morquio syndrome but has also opened the way to elucidation of the basic biochemical defect. Chondroitin sulfate B and heparitin sulfate are excreted in considerable amounts. Although the relative amounts of the two mucopolysaccharides excreted varied from case to case, no distinguishing features could be found between the autosomal recessive and sex-linked recessive forms. Meyer and colleagues made the intriguing suggestion that a failure in degradation is not involved, but rather an overproduction of mucopolysaccharides by races of fibroblasts which do not ordinarily produce them. The presence of an enzy-

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matic block of a more conventional type, that is, like that in other inborn errors of metabolism, remains a possibility. Studies of calcium metabolism revealed questionable abnormalities (Bronner); clinical and pathologic studies would not suggest any such abnormalities as a primary feature.

A simplified test for mucopolysaccharide in urine was described (Dorfman). The inclusions in the leukocytes, first described by Alder (1939) of Switzerland, were the subject of a symposium in honor of Albert Alder on the occasion of his seventieth birthday (Fricker-Alder; Astaldi; Mauri; Grgić). Histochemical studies indicate that the granules contain protein-polysaccharide complexes.

The pathogenesis of the progressive impairment of intellect is not elucidated. However, hydrocephalus, due probably to involvement of the meninges with heavy deposits of mucopolysaccharide, certainly contributes (Bernard). Other clinical features were described by Griffiths and Findlay, Jacobson and Kibel, and Lamy and colleagues. It is now clear that the disease occurs in the Negro, possibly as frequently as in whites, contrary to previous impressions.

182. It may be proper to consider *osteopoikilosis* a generalized disorder of connective tissue. It is hereditary. Furthermore, "spotted bones" due to islands of osteosclerosis are associated with fibrotic lesions in the skin (Mondant).

B. Gene-influenced Diseases.—

183. In *rheumatoid arthritis* Lawrence and Ball studied families of affected probands using a serologic hemagglutination test of the Waaler-Rose type. They found a higher prevalence of rheumatoid arthritis in the families of seropositive probands than in the families of seronegative probands. Interestingly there was no sex difference in the frequency of seropositivity. Lawrence and Ball suggested that their observations may indicate that rheumatoid arthritis is not a single entity. Some seropositive individuals in families of patients with rheumatoid arthritis were free of clinical or radiologic evidence of the disease.

Ziff and his collaborators have also pursued a family study of rheumatoid arthritis using a serologic test, Ziff's inhibition test, which gives almost 100 per cent positive results in cases of rheumatoid arthritis and about 4 per cent in others. A prevalence of 20 per cent positivity was found in first-degree relatives (parents, sibs, and children) of patients with rheumatoid arthritis.

184. The Caplan syndrome (editorial)—a characteristic pneumoconiosis occurring in persons who have the genotype predisposing to rheumatoid arthritis and who are also exposed to coal dust (tuberculous infection may be a third contributing, if not essential, factor)—was described for the first time in the United States (Kantor). The syndrome has been observed in persons exposed to asbestos and to the silica of sand used by boiler-scalers (Campbell) and foundry workers (Caplan).

185. In male patients with *ankylosing spondylitis* the description of an increased frequency of prostatitis and seminovesiculitis (Mason) is of interest

because of the higher incidence in men than in women. If the striking familial aggregation is genetic, the apparently greater penetrance in men may have its basis in this mechanism: genitourinary tract infection and the gene(s) for ankylosing spondylitis may be "necessary and sufficient causes"; both may be necessary and neither alone sufficient.

186. Wagenhals and Burgeson reported on the occurrence of *systemic lupus erythematosus* (SLE) in identical twin sisters. Bloom had observed a 27-year-old woman, with SLE, whose sister had died of the disease at the age of 22. Griffin, Ulloa and Holley reported SLE in father and daughter. The biologic false positive serologic test for syphilis, sometimes an indication of otherwise inapparent SLE, was observed by Cannon in a mother and all of her three daughters and not in the father and two sons.

187. Gout. Goldthwait and colleagues reviewed the clinical records of 225 patients with elevated serum uric acid values (greater than 6 mg. per 100 ml.). Less than half the group had clinically characteristic gouty arthritis and in less than half of the rest did kidney disease, polycythemia, neoplastic disease of the bone marrow, or a family history of gout explain the hyperuricemia. The study again emphasizes the desirability of knowledge about the frequency distribution of serum uric acid in a randomly selected sample. Bloomfield published an annotated bibliography on gout.

188. Perloff and Phelps provided the second autopsy report of the *Werner syndrome:* scleroderma, cataracts, premature atherosclerosis, high-pitched voice from vocal cord changes, impotence and sterility, diabetes, calcinosis circumscripta. The disorder may be an autosomal recessive. The parents were second cousins. At least 3 siblings, the male proband and 2 sisters, were affected. The high frequency of neoplasia, especially sarcoma, was emphasized.

XII. EAR

(*See also* ¶'s *172, 173, 191, 266, 282.*)

189. Deraemaeker published a pedigree of deaf-mutism suggesting sex-linked recessive inheritance and pointed out that one of the pedigrees of Stevenson and Cheeseman is consistent with this mode of inheritance. Parker also described a form of congenital deafness due to a sex-linked recessive gene. He estimated that less than one third of congenital deafness has a hereditary basis. In most, autosomal recessive genes are probably involved. In the autosomal and sex-linked forms there are no recognizable associated abnormalities. In the rare autosomal dominant form, Waardenburg's syndrome, wide bridge of the nose and partly white eyelashes, hair, and skin are associated.

The data and their interpretation published by Stevenson and Cheeseman (1956) concerning hereditary deaf-mutism in Northern Ireland have stimulated great interest. All seem agreed that the data are incompatible with a single,

simple recessive inheritance. Stevenson and Cheeseman suggested multiple recessive genes. Slatis suggested that heterozygosity (dominant genes) may account for some and considered other alternative hypotheses.

In the interpretation of the genetics of congenital deafness nongenetic causes are of interest. The role of toxoplasmosis was suggested by Keleman.

190. Fowler has been studying otosclerosis in identical twins.

XIII. THE ENDOCRINE SYSTEM AND SOME METABOLIC DISORDERS

191. Thyroid. In a family in which congenital deafness was associated with goiter developing in childhood, Morgans and Trotter found that I^{131} uptake was high but part of the I^{131} present after one hour was dischargeable by perchlorate. A partial defect in the organic binding of iodine, perhaps compensated for by increased secretion of thyrotropin, was suggested. The subjects were euthyroid and normally developed. Recessive inheritance was suggested. Clayton and associates also had a family in which euthyroid individuals had goiter and a defect in the organic binding of iodine as indicated by release of thyroidal I^{131} after potassium thiocyanate administration.

192. Parathyroid. The association of moniliasis, *hypoparathyroidism* and adrenal insufficiency, beginning in childhood and often showing familial incidence, has recently emerged as a distinct syndrome. Sometimes hypoparathyroidism is first recognized; in other cases, as in those of Malloy and Woodruff, adrenal insufficiency is the presenting endocrinopathy. Bronsky and colleagues reviewed the evidence on the heritability of idiopathic hypoparathyroidism and pseudohypoparathyroidism. Evidence for a genetic basis of the latter entity is particularly strong.

Jackson reported 6 and possibly 7 cases of *hyperparathyroidism* in two generations of a family. Recurrent pancreatitis was associated in at least 2 of the patients. He suggested that pancreatitis may be secondary to stone formation in the pancreatic duct system.

193. Diabetes mellitus. Steinberg reviewed the genetics of diabetes mellitus. His conclusion was that diabetes is the result of the homozygous state of a single gene and that as many as 5 per cent of the population of the United States are homozygous for the gene. He pointed out that a reliable test for the prediabetic state will be a great boon to genetic analysis. As further assistance he suggested (1) a series of families, selected because both parents are diabetic and without attention to the diabetic state of the offspring, followed until all children are over 60 years of age or dead; (2) a series of families selected because one parent is diabetic and similarly followed.

A test for mild diabetes mellitus which should be explored as a test for the prediabetic state was described by Unger and Madison.

194. Adrenal. Kappas and Gallagher found in adult dichorionic, monozygotic triplets evidence suggesting both genetic and intrauterine influences on the pattern of adrenal steroid secretion in man.

Three phenotypes of adrenal hyperplasia are identified: (1) adrenal hyperplasia with virilism only; (2) adrenal hyperplasia with hypertension; (3) adrenal hyperplasia with electrolyte disturbances. From the behavior of these phenotypically distinct entities in families and from the enzyme defects which have been identified, at least the first two are probably genotypically distinct, although all appear to be inherited as an autosomal recessive. The defect in the first type appears to involve an enzyme in steroid synthesis, so-called "21-hydroxylase." In the second the defect is probably in a different enzyme "11-β-hydroxylase." The defect in the third type is not completely elucidated; 21-hydroxylase seems to be defective in this type also. Eberlein and Bongiovanni suggested that the defect in types I and III is the same. Patients of both types have a defect in hydrocortisone production. However, patients of type III may by "tremendous overactivity" be able to produce enough hormone to keep out of electrolyte imbalance.

The steroid excretion pattern was described in detail in 3 of 6 siblings who suffered from familial congenital hyperplasia of the adrenal cortex manifested as female pseudohermaphroditism (Birke).

Bierich reviewed the subject of the adrenogenital syndrome in children.

Erez and Yenen reported on the occurrence of pregnancy in a woman with the adrenogenital syndrome treated with cortisone.

195. Obesity. Tepperman contrasted the attitude toward obesity 15 or 20 years ago with the present view: Earlier most obesity was called "simple obesity," and was considered to be due simply to overeating. Fat people were all gluttons. The present view, documented in so far as available information will permit, is presented as follows: "Hereditary predisposition to obesity and leanness is accepted as having been well demonstrated in experimental and farm animals, and for the purposes of the arguments persented herein, it is accepted as occurring in human beings. The nature of the genetic message which is decoded to yield either an obese or a lean individual is considered under three main sections: 1) the function of the food-intake-regulating apparatus of the central nervous system; 2) determinants of activity patterns; and 3) possible mechanisms involved in variations in over-all efficiency of food utilization." Among the latter discussed are (a) variations in efficiency of phosphorylation; (b) aerobiosis versus anaerobiosis; (c) variations in energy utilization; and (d) variations in lipogenesis.

XIV. THE EYE

196. Keratoconus occurred in all 4 of two pairs of identical twins (Franceschetti).

197. Congenital glaucoma was discussed by Barkan and Ferguson. It is usually transmitted as an autosomal recessive. Consanguinity was noted. In only about half the cases are both eyes involved and males are affected somewhat more often than females. In one family a parent and child were affected.

This may, of course, still be the recessive form of the disease if the other parent was heterozygous. Associated abnormalities are missing except in the rare genetic syndrome described by Lowe, Terry, and MacLachlan (decreased renal ammonium production, congenital glaucoma, and mental retardation). The canal of Schlemm is present and communicates normally with the veins. The canal of Schlemm can be seen to fill with blood when the jugular veins are compressed. The defect is thought to involve the permeability of the trabeculum to aqueous humor. Intraocular pressure, which is the net result of secretion and drainage of aqueous humor, may not be elevated at birth; secretion by the iris has not yet fully developed. With early diagnosis surgical treatment can give good results.

Bilateral congenital buphthalmos was observed in two sisters (Graham, Crick). The cornea was observed to be cloudy at or soon after birth. This may represent a severe form of the same entity discussed above.

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198. Durham described congenital *Horner's syndrome* in a boy and his father, paternal aunt and uncle, and a first cousin. The boy showed ptosis and pupillary change on the left. The right iris was brown, the left blue. The findings, which are identical with the classic ones of Calhoun (1919), illustrate the role of normal sympathetic innervation of the iris in iris pigmentation.

199. The *Weil-Marchesani syndrome* (short stature, brachydactyly, and spherophakia with subluxation of the lenses) occurred in two brothers (Zabriskie). The parents were first cousins and short. The maternal grandmother was of short stature, wore glasses from early childhood, and had cataract extractions late in life. In one brother, mild pulmonary stenosis, probably of infundibular type, was proved by cardiac catheterization.

200. Andersen and Schultz studied inherited congenital *cataract* in beagle puppies. The genetics is obscure. An affected male transmitted the disorder to 22 of 25 progency, apparently without regard to sex.

Cataract and congenital ichthyosis occurred, probably in syndromal relationship, in two Japanese brothers (Pinkerton).

201. In a case of *von Hippel's disease* there was no recurrence of the original angioma or development of new angiomas in the retina 11 years after diathermy coagulation (Vail).

202. Sidman and Feder did histologic studies of the retina in the recessively inherited disease of C_3H mice, characterized by absence of photoreceptor elements in the adults. They looked on the retinal change as an abiotrophy.

203. Smith and Sorsby found that most *retinoblastomas* are unilateral and sporadic. They estimate that the average risk to subsequent children or to the offspring of the proband is about 4 per cent in such unilateral, sporadic cases.

Bilateral involvement is likely to occur in the "familial" cases. High mutation rates, such as the figure of 2.3×10^{-5} given by Falls and Neel are untenable in their opinion.

204. Jampel and Falls provided a follow-up on a 19-year-old male, the offspring of first cousins, with atypical *retinitis pigmentosa*, acanthrocytosis (thornlike processes on the surface of the red blood cells), and degenerative neurologic disease manifested by ataxia, intention tremor, and athetoid movements. An extraordinarily low serum cholesterol (37 mg. per 100 c.c.) was consistently found. A defect of lipid metabolism was postulated.

205. Graham and Hsia studied a case of unilateral *color blindness.* They quoted Judd (1948) as stating that there are 37 cases in the literature of which 8 have been studied in detail. (See ¶ 28.)

206. Congenital *optic atrophy* was described in three generations of a family (Iverson). It appeared to be inherited as an autosomal dominant, a feature which together with its congenital nature distinguishes it from Leber's optic atrophy.

A complete anatomic study of a case of Leber's optic atrophy (Kwittken) led to the conclusion that there is a primary neuronal degeneration of the retina and optic nerve, with secondary degeneration of the remaining optic system excepting the calcarine cortex. The possibility of associated spinocerebellar degeneration was raised.

207. Myopia seems to have in part a genetic background. However, Gardiner concluded that increase in myopia is greater and commoner in children who refuse animal protein in their diet. Visual deterioration seemed correlated with spurts in physical growth. Visual deterioration seemed to be retarded by providing extra animal protein in the diet.

XV. GENITAL SYSTEM

208. It has become customary to refer, on the basis of "nuclear sexing," to the normal male as "chromatin negative" and the normal female as "chromatin positive." Epstein and colleagues illustrated the usefulness of chromatin sex determination by describing a case of Klinefelter syndrome, one of Turner syndrome, one of female pseudohermaphroditism due to adrenal hyperplasia, and a fourth child in whom sex was intermediate by inspection of the genitals. The application of the technique to the study of intersexes and infertility was described by several authors (Briggs; Briggs and Kupperman; Briggs, Epstein, and Kupperman).

Dykstra described details of the sex chromatin in the smears of buccal mucosa. He suggested that in the male with one X chromosome the heterochromatic portion is a thin sheet oriented in a plane parallel to the optical plane and therefore undetectable with present staining methods. When two X chromosomes are present, the increased thickness of two sheets permits recognition.

Cooper and Cranny found 92 per cent reliability of the blood smear in determination of genetic sex. An extra nuclear mass, "satellite" or "drumstick," was the criterion for recognition of the female. Sansone and Levi also found the leukocyte method satisfactory, as did also Schenk. Briggs raised the interesting question as to whether a genetic factor may explain why some women fall into a "low drumstick count category" rather than a high drumstick category. Intrafamilial similarities of females in this regard are under study.

Davidson and colleagues did nuclear sexing on the leukocytes of "Mrs. K.," a historic case having been the first human chimera identified (on the basis of red cell antigens), and on two other sets of dizygotic twins of unlike sex. In all 5 twins "drumsticks," indicating female nuclear sex, were found. The paper provides no indication of how many dizygotic twin pairs were investigated in order to find these cases.

Ashley and Theiss extended the observations of Hunter and Lennox (1954) who showed that teratomas of the male testis often contain female tissue. Of 25 teratomas Ashley and Theiss found the female chromatin pattern in 7. They studied in all 75 cases of testicular tumor to determine whether the normal testicular tissue had a male chromatin pattern; it did, in all instances.

An increased incidence of chromatin-positive Klinefelter's syndrome in the mentally defective population as compared with the general population was shown by Ferguson-Smith, who found 4 in 325 "male" patients institutionalized because of mental defect. Prader and associates found an even higher incidence of 8 in 336 in a similar survey of feeble-minded boys; not a single case was found among 390 boys of average or high intelligence.

In an 18-year-old phenotypic male Ferguson-Smith and Munro found spermatogenesis up to, and including, the development of mature spermatozoa, despite the presence of female nuclear sex. Gynecomastia and microorchidism (the Klinefelter syndrome) were present.

209. Ashley and Jones studied a child who had female genital morphology, except for enlargement of the clitoris, and apparently normal ovaries, but male nuclear sex.

Milner and colleagues observed 2 siblings with true *hermaphroditism.* A sister and 2 brothers were normal. Both had unilateral undescended testis and hypospadias, as have occurred in almost all previously reported cases. The chromatin pattern was negative. Surgical exploration of both testes revealed ovarian tissue in association with testicular tissue. Surgical separation of the two types of gonadal tissue was easily performed. The combination of testicular nodule, cryptorchidism, and hypospadias suggests the diagnosis. Clayton and colleagues described true hermaphroditism in 16-year-old and 7-year-old siblings who were genetic females. Scrotal testis and ovaries were present in both. Both had hypospadias.

210. Grumbach and Barr reviewed in a comprehensive manner "the present status of research in human sexual anomalies, with particular emphasis on the interpretations that have arisen since the introduction of the cytologic

tests of chromosomal sex." Within the limits of space it is impossible to do justice to this important survey of monographic proportions. Methods of cytologic sexing were reviewed. The importance of distinguishing sex determination and sex differentiation was stressed. The discussion included virilizing adrenal hyperplasia; gonadal dysgenesis, including the Turner syndrome in boys and men; male pseudohermaphroditism with feminizing testes; Klinefelter's syndrome.

The authors described, with illustration, a 7-day-old infant, with *gonadal dysgenesis* and male nuclei with pronounced lymphedema of the extremities and loose edematous folds at the nape of the neck—features described by Ullrich (1949). The male sex chromatin pattern is not associated with all cases of the gonadal dysgenesis syndrome. Of 117 cases in the authors' series 12 were proved female and 15 were suspected female. Familial instances of gonadal dysgenesis are rare; the authors could find only 8 reports of familial occurrence and some of the these are dubious. There were no familial cases in their own series. Reference is made to identical twins, both with gonadal dysgenesis and male chromatin pattern, studied by Turner. Birth rank, season of birth, maternal age, and maternal illness did not seem to be factors. In the discussion, Hoffenberg defended the genetic basis of gonadal dysgenesis. He cited Rossi and Caflish's evidence for heritability of the "pterygium syndrome," a frequent component of the gonadal dysgenesis syndrome (conversely gonadal dysgenesis occurs in perhaps a third of cases of the "pterygium syndrome"). He referred to his recent trigenic theory: "I" for infantilism, "S" for short stature, and "A" for congenital anomalies. (The multiple-linked-gene basis for hereditary syndromes—if a hereditary syndrome this is—seems unlikely for several reasons but cannot be discarded entirely.—Ed.) In reply Grumbach made a useful analogy to Mongolism: in gonadal dysgenesis clear evidence for a genetic factor may be slow in coming; environmental and genetic factors may collaborate in the causation.

Male pseudohermaphrodites with feminizing testes present an interesting situation (Grumbach and Barr). The external genitals are female and the breasts are well developed. The sex chromatin pattern, however, is male. The diagnosis is usually made when labial masses are found to be testes. A hereditary basis is suggested by a high familial incidence. (Marshall and Harder reported the testicular feminizing syndrome in twins who were presumably monozygotic. The nuclear sex was male. Breast development was excellent and the attractive twins had worked as airline stewardesses!) This condition occurs only in males but is transmitted through the healthy mother. The ratio of normal female sibs to affected male plus unaffected male sibs is about the expected 1:1. Concordance and discordance in twins have been reported but zygosity is uncertain. In 16 sibships analyzed by the authors there were 65 affected males. Analysis by the Hogben method would predict 63 affected males, according to a sex-linked recessive or sex-limited dominant hypothesis. The difference is not significant. Since affected males are sterile it is not possible to distinguish between the two genetic hypotheses, unless a family with a sex-linked trait, such as color blindness, is discovered.

The authors present the cases of identical twins, both with the *Klinefelter syndrome* (called by the authors "seminiferous-tubule dysgenesis"). (Holub,

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Grumbach, and Jailer reported separately upon the 17-year-old identical twins concordant for Klinefelter's syndrome. Female chromatin pattern was present in buccal smears and Leydig cells.) In two other families there was more than one affected sib; similar familial cases are reported in the literature.

In the discussion of the paper of Grumbach and Barr, presented at the Laurentian Conference, Gregory Pincus raised the following questions with reference to the Klinefelter's syndrome: If there are genetic females with defective testes, is it possible to find genetic females with functioning testes? If so, would they account for the families in which there are only female children? He suggested examination of the sex chromatin of the fathers of many daughters.

Rathbun, Plunkett and Barr, and Greenblatt also reviewed sex anomalies. Jones and Scott, in a book entitled *Hermaphroditism, Genital Anomalies and Related Endocrine Disorders*, essentially brought up to date Hugh Young's book on this subject. In a symposium held in September, 1957, and published in November, 1958, under the editorship of Robertson Smith and Davidson, many aspects of nuclear sex were discussed.

211. Alslev and Reinwein reported on the familial incidence of what they term the Ullrich-Turner syndrome. The report is also valuable as a description of the syndrome in males. They quote Rossi (1951) as finding in 197 cases the following incidence of malformations: 41 per cent stunted growth, 34 per cent hypogonadism, and 9.6 per cent cardiac malformation. The report concerns itself mainly with two chromatin negative brothers aged 16 and 19 years. The features were as follows:

	(1)	(2)
Cryptorchidism and testicular hypoplasia	+	+
Dwarfism	+	+
Pterygium colli	+	sl.
Hypoplasia of mandible	+	+
Low-set ears	+	+
Epicanthus	+	+
High arch palate	+	+
Flat chest	+	+
Congenital heart disease	+	+
Hereditary edema of legs	+	+

212. Cantwell, Johnston, and Zeller, and Johnston, Zeller and Cantwell have studied *sex anomalies in swine.* There seem to be some interesting parallels to intersex conditions in man. Swine with only testes but a female chromatin pattern resembling Klinefelter's syndrome were described. This and other intersex states are inherited in swine. (Cryptorchidism is also inherited.) The mode of inheritance is probably not simple autosomal recessive.

XVI. MUSCLE

213. Drager, Hammill, and Shy found 30 members of six generations of one family affected by *paramyotonia congenita*, the disease described by Eulenberg. The characteristics of the disease are (1) inheritance as an autosomal

dominant with high penetrance, (2) myotonia, increased by exposure to cold, (3) intermittent flaccid paresis, not necessarily dependent on cold or myotonia, (4) lability of serum potassium; nonprogressive nature, and lack of atrophy or hypertrophy of muscles. The authors suggested that Gamstorp's adynamia paralytica episodica may be the same disease.

214. Caughey claimed that *myotonia congenita* is merely a variant of *dystrophia myotonica.* Two "older members have undoubted dystrophia myotonica, whereas a member of the second generation presents a picture of myotonia congenita." Although it seems that patients with dystrophia myotonica may pass through a stage in which only muscle hypertrophy and myotonia are present, it remains possible that there is a distinct genetic entity of pure myotonia congenita.

Between 1945 and 1956 Klein collected 229 cases of dystrophia myotonica (Steinert's disease) and 10 of myotonia congenita (Thomsen's disease) in Switzerland. He concludes on the basis of this unusually large experience that the two diseases are separate and distinct. Because the testicular lesions of Steinert's disease resemble those of Klinefelter's syndrome, because Klein found slight preponderance of "males," and because pooled data from the literature yield a sex ratio of about .536, it was of great interest to study nuclear sex in these individuals. (Marshall and Thomas studied the nuclear sex chromatin pattern in 14 males and 4 females with this disorder. In all cases the chromatin pattern was appropriate to the apparent sex.)

In the Steinert data there was the usual "anticipation" which Klein thought was real. He made no attempt to test the various factors which might result in factitious "anticipation." It is hoped that Klein will examine many other factors in this large group of cases.

In pharmacologic tests on goats with myotonia congenita, Tum-Suden appears to have excluded the chemical mediator system as the site of the basic defect. Cholinesterase levels in myotonic tissue were normal.

Jarcho and Tyler described a 39-year-old woman who probably had myotonia congenita, as did several members of her family, but did not have symptoms from it until myxedema was precipitated by thyroidectomy. They use the term pseudomyotonia for cases of myotonia due solely to myxedema and provide a useful list of features distinguishing pseudomyotonia from myotonia congenita. Several myotonic members of the family they described showed hyperkeratosis palmaris et plantaris.

215. Studies (Soffer) of adrenal cortical function in 2 cases of dystrophia myotonica and one case of the facioscapulohumeral type of *muscular dystrophy* seem to have contributed nothing to the understanding of the diseases. Manning and Cropp found that the electrocardiogram showed changes in the majority of cases of juvenile *pseudohypertrophic muscular dystrophy* (28 cases) and none of adult *facioscapulohumeral* type (10 cases). The ECG might be a useful differential diagnostic point. Gailani, Danowski, and Fisher also studied the heart in muscular dystrophy. They found that mild exercise and abdominal compres-

sion raised right ventricular diastolic pressure, suggesting the presence of latent heart failure. They suggested that the large R wave in the ECG is a variety of conduction defect. See review, by Tyler, of muscular disorders of childhood. Stevenson presented further data on muscular dystrophy in Northern Ireland. Kloepfer and Talley observed autosomal recessive inheritance of the Duchenne type of muscular dystrophy (pseudohypertrophic). From their report some features such as age at onset and rate of progression of the disease suggest phenotypic differences from the usual sex-linked recessive form.

216. Lafuente and colleagues did detailed studies of a case of *familial periodic paralysis* and concluded that sequestration of potassium in muscle cells is the primary physiologic fault.

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217. Blondheim and associates described a simple test for differentiating *myoglobinuria* from hemoglobinuria. Eighty per cent saturation of the urine with ammonium sulfate results in complete precipitation of hemoglobin whereas myoglobin remains largely in solution. Other differentiating features, useful in the diagnosis of paroxysmal myoglobinuria (hereditary paroxysmal rhabdomyolysis) are reviewed.

218. Myopathies in dogs were reviewed by Meier with report of cases. Some worth-while literature on hereditary disorders is referred to.

XVII. NEOPLASMS

For the most part neoplastic diseases are discussed with the particular organ system which is the primary site. See ¶'s 23, 121, 125, 126, 128, 157, 164, 203, 208. In addition, a few are discussed here.

219. Stephens and colleagues restudied a large Mormon family in which they had found in 1949 a strikingly high frequency of *breast cancer*. On re-examination 9 years later they found 11 new cases of breast cancer or tumor—one of them in an 87-year-old man. Some familial aggregation is to be expected occasionally by chance alone. In this family, aggregation seems too marked to be explicable on the basis of chance. The findings are consistent with sex-influenced autosomal dominant inheritance. If such a gene is segregating in families such as this, it may be necessary to postulate etiological heterogeneity in breast cancer which clinically seems homogeneous. Certainly familial aggregation is not impressive in other data.

A monograph by Anderson, Goodman, and Reed presented the results of their study to see if there is any familial aggregation for breast cancer or any familial tendency to cancer in general, site not specified. An early part of the book discussed methodology in a very helpful manner. They point out interestingly the rather modest concordance rate in monozygotic twins which might be found despite a strong hereditary determination (pp. 36-37). The reason is, as was pointed out by Gorer (1953), that concordance in identical twins can ap-

proach 100 per cent only as the correlation of age at onset in the twins approaches 1. Assuming (1) that each proposita had been interviewed at the time of first diagnosis of breast cancer, (2) that each proposita had a monozygotic (female) co-twin, (3) that breast cancer were absolutely and completely genetically determined with full penetrance, and (4) that the age at diagnosis of breast cancer in the co-twin bears no relation to the age at diagnosis in the proposita but shows the same distribution as in a large group of cases of breast cancer, the authors calculated that at age 50 there would be less than 30 per cent concordance.

220. Foote, Albin, and Hall observed chordoma in the sacral area in middle-aged siblings. They could find no other report of familial occurrence.

221. Beolchini, Gianferrari, and their colleagues, from a study of the families of 199 probands with uterine cancer, could find no evidence for a significantly higher familial incidence than in controls.

XVIII. THE NERVOUS SYSTEM, INCLUDING MENTAL DEFECT AND PSYCHIATRIC DISORDERS

(*See also ¶'s 33, 41, 42, 111, 117, 201, 204.*)

222. Many genetic disorders are discussed in *Neuropathology*, a comprehensive treatise by Greenfield and other authors, which appeared in 1958. Metachromatic leukoencephalopathy is a disorder of note since it is another heritable central nervous system disease of which telltale evidence—metachromatically staining material—may be found in the urinary sediment.

deVries, van Bogaert, and Edgar described two sibships, from Jewish families, containing multiple cases of a degenerative brain disease of infancy which probably is in the leukoencephalopathy category but has distinctive features.

223. Vogel provided a valuable contribution to the genetic basis of the normal electroencephalogram in a study of 110 monozygotic and 98 dizygotic twin pairs.

Comparative genetic pathology: 224. Anderson and Harman concluded that of two recessive lethal mutations in animals, the wabbler-lethal in the mouse is a developmental myelin defect occurring in CNS tracts undergoing active myelination, whereas the ataxic rabbit mutation results in a degenerative process involving already well-myelinated parts of the CNS.

Lipidoses: 225. (*See ¶ 17.*) Crocker and Farber reported on a study of 18 patients with *Niemann-Pick disease*. Six were of Jewish ancestry. At least 5 had affected siblings. Death occurred at ages varying from 4 months to 19½ years. Of 3 still living one was 17.8 years old. The 4 of the 18 probands with an atypically prolonged course and less marked visceromegally were of French

Canadian Catholic ancestry and were descendents of the inhabitants of a small area in Nova Scotia near Yarmouth. One instance of consanguinity was known and the occurrence of the same family name suggested kinship of these 4 cases. This could represent a genetically distinct entity or, alternatively, the difference may have been due to modifying effects of the particular genotype shared in part by these individuals.

A 2-year-old child developed a soft, tender mass below the left ear. On surgical drainage only a small amount of pus, growing Staphylococci, was found. A malignancy was considered likely but biopsy showed an admixture of inflammatory and Niemann-Pick cells. The condition progressed to involve a large part of the face and forehead. Radiation therapy appears to have helped.

Although the spleen, liver, lymph nodes, bone marrow, and, of course, the ganglion cells of the brain and retina were predominantly involved, no tissue escaped in severe late cases. Examination of the blood in some patients revealed vacuoles in the circulating lymphocytes. At present there is no method for identifying persons heterozygous for the "recessive" gene of the Niemann-Pick disease. The homozygotes have a generalized disturbance of sphingomyelin.

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226. Gartner and Bronstein described the anatomic findings in 5 cases of infantile cerebroretinal lipidosis (infantile *amaurotic idiocy*; Tay-Sachs disease).

In juvenile amaurotic idiocy Rayner and Böök confirmed and extended the earlier observations of Bagh and Hortling (1948) and Rayner (1952) on leukocyte inclusions in patients (homozygotes) and relatives (heterozygotes). The ordinary Giemsa-stained blood smear is adequate. Their data were as follows:

		AFFECTED		AVERAGE % VACUOLATED
	N	OBS.	EXPECTED	CELLS
Homozygotes	29	29	29	17.7
Parents (heterozygotes)	43	31	43	2.1
Normal sibs (1/3 normal; 2/3 heterozygotes)	46	18	31	1.6

Kivalo and Kivalo also found vacuolization of lymphocytes in healthy relatives of patients with juvenile amaurotic idiocy and performed electron microscopic studies. Apparently the inclusions have not been found in infantile amaurotic idiocy (Tay-Sachs disease). Genetic and biochemical differences may be supported by these observations. The form of the disease in which inclusions have been found is that with which Bielschowsky's name is associated in the literature.

Cogan makes a plea for the use of eponyms in connection with amaurotic family idiocy. Although chemical differences have not yet been worked out in any detail, ophthalmologic features indicate differences in the separate types which are appropriately indicated by the names of Tay-Sachs, Batten-Mayou, and Spielmeyer-Stock-Bielschowsky. Age differences tend to show overlap.

Aronson and colleagues studied longitudinally multiple serum and spinal fluid chemical characteristics in 19 consecutive patients with Tay-Sachs infantile

amaurotic family idiocy (AFI) and, for comparison, in single cases of Niemann-Pick's disease (NPD) and diffuse sclerosis. During the state of rapid anterior horn cell involvement serum aldolase became significantly elevated, apparently because of wasting of skeletal muscle, but returned later to normal levels. A similar pattern was observed in NPD which has a similar pattern of cellular CNS involvement with secondary lower neurone degeneration. Serum glutamic-oxalacetic acid transaminase was consistently and markedly elevated during the entire course of all cases of both AFI and NPD. The child with diffuse sclerosis showed, at the most, insignificant elevations of serum transaminase. Spinal fluid transaminase was depressed in diffuse sclerosis. In all three conditions serum neuraminic acid was elevated. An abnormal pattern of the protein linkage of neuraminic acid was suggested. The gamma globulin in spinal fluid and blood was depressed.

Whereas the hyperaldolasemia was thought to be of muscle origin, the transaminasemia was thought to be of both muscular and nervous origin. It was noteworthy that in diffuse sclerosis, a disease predominantly of the gray matter, hypertransaminasemia was not observed.

Huntington's chorea: 227. Reed and Chandler estimated that the frequency of persons with recognized chorea is 4.12×10^{-5} and that the total frequency of persons heterozygous for this dominant gene is 1.01×10^{-4}. They found a sib-sib correlation coefficient of 0.28 for age at onset and 0.47 for age at death. Surprisingly there was no significant sib-sib correlation for onset-death interval. No difference in social status or marital status of choreic individuals was demonstrable.

Some patients with Huntington's chorea had complete control of choreic movements when reserpine was given (Kempinsky). Drowsiness and psychomotor retardation could be counteracted with some success with D-amphetamine. However, deterioration of other aspects of behavior occurred in some patients on reserpine.

Huntington's chorea represents one of the most challenging problems in genetic counseling. Methods for identification of presence of the gene before it expresses itself in classical form would be of tremendous value both to affected and to unaffected. Baroff, Falek, and Haberlandt performed a battery of tests of psychomotor function in the first degree relatives of patients with Huntington's chorea. A heterogeneity in the results suggests the possibility of identifying the clinically asymptomatic carrier. Decline in function was observed in some on retesting after two years. As the authors appropriately emphasize, only subsequent developments in these individuals will permit conclusions on the significance of the differences observed.

Parker gave a fairly detailed review of Huntington's chorea based on his experiences in Queensland, Australia.

Spinocerebellar degeneration: 228. Fitzgerald and Hyland suggested that the 74 cases encountered in adult general hospital practice (Toronto General Hospital) could be divided into two groups: (1) those which develop in child-

hood with manifestations indicating the spinal cord as main site of involvement, and (2) those which develop in adult life with predominant cerebellar involvement. In 10 of 62 adult patients presenting a predominantly cerebellar type of spinocerebellar degeneration there was a family history of the disorder. The first group included cases of Friedreich's ataxia (2 of 8 had cardiac disease). Two others probably should be classed as having the Roussy-Lévy syndrome or hereditary areflexic dystasia; the early marked progression was not observed in these cases. Two cases of the spinal cord type, in brothers, should be classified as familial spastic paraplegia. The possible contributing role of other factors such as alcoholism, malnutrition, and malignancy was considered.

Malamud and Cohen described a sex-linked recessive form of cerebellar ataxia. The disease began in the first year or two of life with ataxia, dysarthria, and intention tremor and progressed to extrapyramidal signs, mental deterioration, and sometimes optic atrophy and myoclonic epilepsy. Changes in the basal ganglion as well as the cerebellum were described.

In the cases labeled Friedreich's ataxia, reported by Sylvester, a father and 6 of 9 children were affected; optic atrophy and nerve deafness were present in addition to the spinocerebellar disease.

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Phacomatoses: 229. Boder and Sedgwick wrote about the syndrome of cerebellar ataxia, oculocutaneous telangiectasia, and frequent pulmonary infections. The telangiectasia of the bulbar conjunctiva was a progressive dilatation of the smaller vessels simulating conjunctivitis. Similar telangiectasia developed in the butterfly area of the face, the palate, the neck, the antecubital and popliteal spaces, and the dorsum of the hands and feet. Frequent sinus and pulmonary infection progressed to bronchiectasis in some. Ataxia was first noted when the children began to walk. Autopsy revealed diffuse cortical cerebellar atrophy and dilated venules in the cerebellar leptomeninges and white matter. The authors suggested that the disease be considered a phacomatosis (van der Hoeve's term for a group of conditions, specifically, neurofibromatosis, tuberous sclerosis, von Hippel-Lindau's disease, the Weber-Sturge syndrome). Eight cases in five sibships were described. This syndrome is sometimes referred to as the Louis-Bar syndrome, or cephalo-oculocutaneous telangiectasia.

230. Peterman and colleagues at the Mayo Clinic studied 35 cases of encephalotrigeminal angiomatosis (Sturge-Weber disease): venous angioma of the leptomeninges of the cerebral cortex with ipsilateral angiomatous lesions of the face. Of the 35 patients 31 had a convulsive disorder, 22 had an abnormal skull x-ray, 19 had mental retardation, 13 had ocular involvement, and 11 had spastic hemiplegia. In 30 there were angiomas of the skin elsewhere than on the face. The literature was fully reviewed by the authors. They emphasize the importance of early diagnosis; neurosurgical techniques have evolved to the point that cortical excision or even hemispherectomy is feasible. The cerebral convolutions undergo calcification which has the pattern characteristic of the gyri. The calcification is apparently secondary to ischemic changes. Familial aspects were not discussed. In reporting a case with necropsy Falkinberg,

Silver, and Kay stated that this was only the eighteenth case in the American literature and suggested that the disorder is much rarer in the United States than in Europe. Clinical experience and the report of Peterman and colleagues make it clear that the disease is by no means rare in the United States and probably fully as common as in Europe.

231. Mavor and Schumacher presented a case report of tuberous sclerosis.

Radicular and peripheral nerve involvement: 232. Primary amyloidosis was discussed by Chambers, Medd, and Spencer, with special emphasis on the neurological aspects.

233. Reimann and colleagues followed up a large family originally reported in 1937 to have myelodysplasia. In the light of autopsy findings in one case and the advance in understanding of related entities in the last 20 years they suggested that the disease in this family falls into the category designated *hereditary sensory radicular neuropathy.* Sensory loss affecting pain more than touch and temperature more than pain was a characteristic. The patients developed trophic ulcers of the feet, pedal osseous necrosis, and similar less severe involvement of the hands. Harelip, cleft palate, and epilepsy occurred in several members of the family.

234. Norstrand and Margulies described *Charcot-Marie-Tooth's disease* in three generations, apparently transmitted as a dominant. Gastrointestinal symptoms in the form of chronic diarrhea, nausea, and vomiting were striking. Degeneration of the lateral horn area of the spinal cord was discovered at autopsy. Stark also described a large family with many affected members.

235. Ashenhurst and colleagues described *Refsum's heredopathia atactica polyneuritiformis* in 3 siblings. The features included (1) atypical retinitis pigmentosa, (2) chronic polyneuritis affecting peripheral parts of the limbs, (3) high spinal fluid protein, (4) ataxia, nystagmus, and other cerebellar signs, (5) sometimes ichthyotic skin changes, and (6) electrocardiographic changes and sudden death.

Others: 236. Kuru, a newly discovered neurological disease affecting the Fore people in New Guinea, may have a genetic cause. A toxic effect, such as by an alkaloid or heavy metal in the food is the principal alternative hypothesis. Extensive studies have been performed by Sir Macfarlane Burnet and his group at the Walter and Eliza Hall Institute in Melbourne. More females than males are affected. The disease does not have its onset until after the age of 5 years, sometimes not until after 45 years of age. The first symptom, tremor of the trunk, head, and extremities, is aggravated by excitement. Urinary and fecal incontinence, extreme ataxia, decubitus ulcers develop and the patient usually dies in 3 to 6 months of starvation and intercurrent infection. Intellect is apparently unimpaired. Pathologically, widespread neuronal degeneration, par-

ticularly of the sensory, cerebellar, and extrapyramidal systems, is described. There is no evidence of an infective process and no leukocytosis or perivascular cuffing. According to the natives, the disease has been known to be present in the tribe for 20 or 30 years.

237. Lamy and colleagues described a case of *congenital generalized insensibility to pain* in a 16-month-old infant. The disorder was discovered because of the development of cuts of the tongue when the first teeth erupted. At 26 months it seemed that some sensation was present. A detailed review of the literature was provided. The authors thought a genetic factor might be involved. Of 40 reported cases, 21 patients were male, 19 female. There are a few reports of multiple affected sibs and of parental consanguinity.

238. Trembling of the chin, apparently transmitted as an autosomal dominant, was reported in 8 members of three generations of a family (Wadlington). There was no associated neurological or other abnormality. Anxiety or emotional upset was a trigger mechanism and tranquilizing and anticonvulsant drugs reduced the attacks. The attacks were observed as early as 2 months of age.

239. Tyler described a large Negro family in which 27 members in seven generations were affected by the *Pelizaeus-Merzbacher disease:* cerebral diplegia characterized by early development of nystagmus, ataxia, and spasticity. The genetic behavior was that of a sex-linked recessive trait. About half the females had affected sons. Affected children were referred to as "head nodders" or "eye waggers" because of the constant nystagmus and side-to-side head tremor which was noted as early as 8 days after birth.

240. Familial dysautonomia is characterized by Jewish ancestry, diminished tearing, increased sweating, cold hands and feet, paroxysmal hypertension, paroxysmal hypotension, corneal anesthesia, etc. (McKendrick). In only about one-third of cases are there other affected members of the family.

241. Spastic quadriplegia combined with congenital ichthyosiform erythroderma and oligophrenia has, prior to the report of Blumel, Watkins, and Eggers and that of Link and Roldan, been reported only from Sweden, by Sjögren and Larsson (1956, 1957), who suggested that all their cases (28 in number) were derived from the same mutation, occurring about 600 years ago and that about 1.3 per cent of the population of the North of Sweden is heterozygous for the mutant gene.

242. Curtius, who in 1933 wrote on heredity in *multiple sclerosis,* reviewed recent information on the subject. Whereas the incidence of multiple sclerosis in Western Europe, United States, and Canada is 1.3 to 6.7 per 10,000, Behnke (1957) found an incidence of 62 ± 4.6 per 10,000 among relatives of patients with multiple sclerosis. There appears to be an increase in parental consanguinity. Curtius found reports of 32 monozygotic twins with multiple sclerosis

in at least one twin; fourteen pairs were concordant. His conclusion is that there can be no doubt that genetic factors play a part in multiple sclerosis.

Mental defect: (*See also* ¶'*s 33, 43, 107, 110, 181, 197.*) *243.* In an extensive study Hanhart concluded that *microcephaly* is a heterogeneous state in which there is one entity, microcephaly vera, inherited as an autosomal recessive. Thirty-five cases of the latter type were found in 23 sibships; the analysis by Weinberg's sib method was consistent with recessive inheritance.

244. Masland provided a comprehensive review of the status of research in mental defect. The methods and results of investigations of the genetic factors are well surveyed. His Table 3 gives a useful résumé of lipid abnormalities in seven demyelinating diseases all of which are probably at least partially genetic in determination. Essentially the same material, supplemented by a discussion of psychological and cultural factors by his co-authors, appeared in a book entitled *Mental Subnormality* by Masland, Sarason, and Gladwin.

Allen, in reviewing work on the genetics of mental deficiency, referred to the demonstration of excessive urinary excretion of beta-amino-isobutyric acid by Mongoloid idiots.

245. Carter and Maley claimed improvement from oral administration of calf pituitary extract to *Mongoloid* children—a treatment first suggested by Benda. Three patients developed a normal I. Q. range and lost some Mongoloid stigmas. Although it is the opinion that pituitary extract would be destroyed before absorption in the gastrointestinal tract, a uniform response in eosinophils suggested that absorption did, in fact, occur.

In a series of 48 Mongoloid infants less than 1 year old Caffey and Ross found four characteristic features of the pelvic x-rays: (1) bilateral flattening of the lower edges of the ilium, (2) bilateral widening and flaring of the iliac wings, (3) bilateral diminution in caliber, with gradual tapering, of the ischial rami, (4) bilateral coxa valga. Norma Ford Walker summarized the use of dermal configurations in the diagnosis of Mongolism.

Baroff reviewed current concepts of the etiology of Mongolism. He concluded that the following features "point to a gene-specific mechanism": (1) twin data, specifically the marked difference in concordance between monozygotic and dizygotic twins; (2) the familial incidence, especially the birth of a Mongoloid child from a Mongoloid mother; (3) dermatoglyphic similarities between Mongoloid persons and unaffected sibs and parents. On the other hand, the low familial incidence and the striking association with maternal age suggest the collaboration of other nongenetic factor(s).

Minor differences in vitamin metabolism in Mongoloid as compared to normal children were described by Gershoff and colleagues.

Franklin gave advice on the care of the Mongol baby, particularly on the difficult matter of assisting the parents' adjustment to the affected infant.

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246. Allan and others in collaboration with Dent found in a severely mentally defective brother and sister a specific gross disorder of amino acid metabolism not present in the parents (who were not related) or in two unaffected sibs. There was constantly excreted in the urine a large quantity of a new and still unidentified substance. There were also minor changes in the pattern of amino acids excreted. Both children had marked changes in the EEG (fits occurred in one) and a heart murmur which it was thought might indicate ventricular septal defect. In both the hair was brittle. The abnormal substance, discovered on chromatograms, was present in low concentration in the plasma but high concentration in the cerebrospinal fluid. Westfall subsequently identified the abnormal metabolite as arginosuccinic acid.

Psychiatric disorders: 247. Rainer and Kallman discussed the role of genetics in psychiatry. Since ultimately the hereditary factor in mental disease will find its explanation in biochemical mechanisms, Kaplan's review of biochemical studies in schizophrenia is pertinent. However, Kaplan in concluding "stated with regret at this point that available data are either disputed or in need of further corroboration." Slater discussed "the monogenic theory of schizophrenia."

248. Sutton and Read described a young child with autistic symptoms in whom there appeared from L-tryptophane loading tests to be a decreased ability to metabolize tryptophane via the 5-hydroxyindole pathway. The anticipated increase in urinary 5-hydroxyindole acetic acid did not occur. (Such increases may occur only in children, not in adults.) It was suggested that the mental aberration was the result of altered ability to maintain normal brain serotonin levels. Physical and intellectual development were normal or advanced. The only evidence that a genetic defect was involved was the finding in one sibling of an abnormal urinary amino acid excretion pattern like that in the proband.

249. Ginsburg presented a highly thought-provoking, informative, and critical review of "genetics as a tool in the study of behavior." He points out that in a crude way we have long known "that particular kinds of behavior are correlated with particular genetic backgrounds." Further elaboration along these phenotypic lines will be of very limited profit. "This may be valuable information for the marriage counselor but hardly for the scientist." It is necessary to analyze gene action, the links in the chain connecting genotype and phenotype. He points out that "treatment" can be logically and most effectively applied when these intermediate steps are known. The work already completed on the biochemical defects in audiogenic convulsive seizures in mice are promising for possibilities in the analysis of gene action. Aggressiveness is a universal mammalian behavioral trait which shows genetic variability and should be susceptible to analysis in terms of the mechanism of gene action. "The complexity of the behavioral repertoire of the dog and man's long familiarity with it and tendency to anthropomorphize about it make this animal a strategic object for the study of genetic influences."

XIX. THE SKELETON

(*See also Section XI, Connective Tissue.*)

250. By roentgenologic measurements alone, Ceballos and Rentschler could differentiate male and female skulls with 88 per cent accuracy. Rosler studied familial similarities in the relative length of the fingers.

251. "*Vitamin D–resistant rickets*" is a term which should be abandoned as rapidly as the separate entities which constitute the group can be identified. The group includes Albright's tubular acidosis, cystinosis, the idiopathic de Toni-Debré-Fanconi syndrome, hereditary hypophosphatemia, and hereditary hypophosphatasia (Lamy, Royer, and associates). The classification of the family described by Christiansson is unclear. An affected mother and her 3 affected children showed normal serum phosphorus; alkaline phosphatase was abnormally high. The bone disorder tended to improve spontaneously at puberty. In one of the children, however, onset did not occur until after puberty. The possibility that some cases of adult osteomalacia are on a genetic basis is, therefore, raised. High doses of vitamin D are used in treatment.

With Salter, Donald Fraser provided a useful outline of rickets:

1. Vitamin D deficiency rickets
2. Chronic renal insufficiency ("pan-nephritic osteodysplasia")
3. Renal tubular disorders
   a. Hypophosphatemic vitamin D–resistant rickets
   b. Same, with aminoaciduria
   c. Same, with aminoaciduria and acidosis
   d. Same, with hyperglycinuria
   e. Cystine storage disease
   f. Miscellaneous
      (1) Oculocerebrorenal syndrome of Lowe (1952)—glaucoma, mental defect, acidosis, aminoaciduria, hypophosphatemic rickets. (This disorder has been described only in males.) See ¶197.
      (2) Hepatolenticular degeneration
      Etc.
4. Miscellaneous
   a. Hypophosphatasia

252. The "genotypic chondrodystrophies" were discussed by Lamy and co-workers. This area is confused and confusing. Some forms are clearly recognizable from the general group: (1) Achondroplasia of Parrot (chondrodystrophia fetalis of Kaufmann). The condition is usually inherited as an autosomal dominant but there are many sporadic cases which appear to represent new mutations. (2) Hypophosphatemic rickets is usually adequately identified by the rachitic changes in the long bones and the low serum phosphate. The disorder is a sex-linked dominant (or intermediate) in many pedigrees; affected males have only affected daughters. (See ¶103.) (3) The Hurler syndrome

("gargoylism") is identified by the visceral involvement and confirmed by demonstration of mucopolysaccharides in the urine (see ¶181). (4) Morquio's disease (called a "dysplasie spondylo-épiphysaire génotypique" by Maroteaux and Lamy) is identified at a glance in the full-blown classical case because of the typical features which have been displayed by many published photographs: dwarfism, disproportionately large hands and feet, genu valgum, short trunk with high shoulders, pigeon breast. Typically the transmission is as an autosomal recessive. (5) Hypophosphatasia. (6) The Ellis-van Creveld syndrome in which chondrodystrophy is associated with polydactyly, dystrophy of the nails and teeth, and congenital heart disease (usually single atrium) is a rare autosomal recessive trait. Fusion of the hamate and capitate bones of the wrist is a pathognomonic feature.

After separating these entities one is left with many other disorders which cannot be convincingly catalogued: the metaphyseal dysostosis discussed by Maroteaux and Lamy and resembling hypophosphatasia; Silfverskiöld's disease; Léri's "pléonostéose," and so on.

253. Caffey wrote about the radiologic changes in the pelvis and lumbosacral spine in *achondroplasia*. Often the changes are more definite than those in the long bones. The ilium is shortened especially in the caudal segment of the wing and the body, below the posteroinferior iliac spine. The greater sciatic notches are reduced to narrow, deep clefts. In the lumbar spine excessive cartilage is shown by the increase in the intervertebral spaces. The bones of the lumbar vertebrae tend, in the achondroplastic spine, to taper downward. Not only is the spinal canal flattened transversely but also markedly in the anteroposterior plane because of shortness of the pedicles. Neurological deficits are to be expected because the spinal canal is too small for its contents. Decompression laminectomy may be necessary in some cases.

Nattrass reported on a father and mother with classical achondroplasia who produced a child affected with achondroplasia of average severity. The author's interpretation of the genetics of achondroplasia is probably erroneous. He seems to think that achondroplasia is a recessive and that all children of two achondroplastics must be affected. In both parents he reported upon, the cases were sporadic—probably new mutations. The form of disease they show is usually dominant. One would, therefore, expect offspring in the proportions of one very severely affected homozygote, two heterozygotes affected with average severity, and one normal.

Gates came to the conclusion that African Pygmies are achondroplastic dwarfs. Although there are at least superficial similarities, it is unlikely, in our opinion, that the Pygmy state is monogenic or that the basic aberration is identical with the pathologic state, classical achondroplasia. It would be of interest to look, in Pygmy infants, for the changes in the pelvic bones, described by Caffey as nearly pathognomonic for achondroplasia (see above).

254. "*Congenital curly toes*," bent toes similar to the clinodactyly and camptodactyly seen in the hand but apparently not genetically related, were

described by Sweetnam. No reference to a possible heritable nature was made. Treatment with over-and-under strapping seemed to have no effect.

255. Carter and Sweetnam observed a family with multiple cases of recurrent *dislocation of the patella.* The entire knee joint and often other joints as well were lax in these individuals and several members of the family without history of dislocation of the patella had loose-jointedness. The pattern of inheritance was that of a dominant.

256. Carpal bossing (*carpe bossu*), a frequent phenomenon, is merely a prominence produced by a double beak between the third metacarpal bone and the capitate bone of the wrist (Larson). The only practical consideration is that carpal bossing is not related to a single traumatic episode (the incidence does increase with age) and cannot be the basis for disability claims. Both heredity and occupational strain have been postulated in the etiology. Symptoms are rarely present but when they do occur are attributable to irritation from slipping of the extensor tendons over the prominence. Reflex vasomotor spasm may also occur.

257. Esteve observed *idiopathic scoliosis* starting before puberty in both of identical twins.

258. Under the designation *familial osteoarthropathy of the fingers* Allison and Blumberg gave an excellent description of the type of avascular necrosis of the phalanges of the hands to which the name of Thiemann is sometimes attached. Painless deformity at the proximal interphalangeal joints began in childhood or adolescence. It was inherited, in their family, as an autosomal dominant with strong penetrance. A consanguineous mating between two affected persons resulted in 2 of 6 offspring who had more severe deformity of the hands than any of the others. These were thought to represent homozygous dominants.

259. In *multiple epiphysial dysplasia* (Barrie; Freiberger) the changes in the hips and knees are especially likely to produce symptoms, but the ankles, hands, spine, shoulders, and elbows have also been affected in some cases. The patients tend to be short but are rarely markedly dwarfed. The fingers are short and stubby and the knees may be knobby from enlargement of the epiphyses. As Barrie and colleagues state, "Osteoarthritis is an inevitable complication, beginning, as may be expected, in early adult life." The condition usually behaves as an autosomal dominant. The spine is rarely involved; in cases with spinal involvement differentiation from the Morquio syndrome may be difficult.

260. David and Palmer described *familial metaphysial dysplasia* in two families. Increased density of bones suggested atypical Albers-Schönberg disease.

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261. Congenital dislocation of the hip has been considered to be inherited as a sex-influenced autosomal dominant. The condition occurs about five times more commonly in females than in males. Dysplasia of the acetabulum, which is abnormally shallow, is the anatomic substrate of the dislocation; it occurs more commonly than recognized dislocation. Record and Edwards suggested that the inheritance of congenital dislocation is in fact polygenic. The fact that the pelvis shows appreciable sexual differences, even as early as the third month of fetal life, may make it unnecessary to postulate specific sex-linked genes to account for the fact that as few as 15 per cent of cases occur in males. The left hip is more often affected. African peoples may have greater resistance to congenital dislocation because of differences in the depth and inclination of the acetabulum. Important environmental influences, such as breech delivery and winter delivery, were demonstrated. Because the degenerative changes are likely to occur in these poorly engineered hips, congenital dislocation of the hip and the dysplasia which underlies it represent one mechanism for genetic determination of osteoarthritis of the hips.

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262. Boyd and Sage described their experience with 15 cases of congenital *pseudoarthrosis of the tibia.* A genetic basis was not commented on nor did they see it apparently in osteogenesis imperfecta—at least cases of pseudoarthrosis in association with osteogenesis imperfecta were not included.

263. Mead, Lithgow, and Sweeney reported on 68 patients with *arthrogryposis multiplex congenita* of whom 12 had been followed from infancy into adulthood. The series included 2 sets of identical twins in which only one was affected; Hillman and Johnson had previously reported two sets of identical twins with discordance. The twin experience plus the negative family history makes a genetic basis unlikely.

264. Maffucci's syndrome (dyschondroplasia like that of Ollier's disease and multiple hemangiomas) was discussed by Marberg and associates and by Bean (¶4). Although this is clearly a congenital malformation, no multiple cases in the same family have been reported, it seems. Lymphangiectasis, phlebectasia with formation of phleboliths, and pigmentary changes in the skin also occur. Sarcomatous degeneration is fairly frequent.

265. Cockshott and Omololu described *congenital posterior dislocation of both radial heads* in a family. Enell and Pehrson described three cases (2 sibs and a cousin) of *osteopetrosis* in a rather highly inbred family. The disease was of the early severe form, inherited as an autosomal recessive. Mau reviewed *juvenile osteochondroses.*

266. Gedda and co-workers described 17-year-old MZ twins concordant for *torticollis* due to wedgelike deformity of cervical vertebrae. Thoms described two cases of *cleidocranial dysostosis* with special features: (1) osteosclerosis with a tendency to fractures, and (2) bilateral coxa valga. Coxa vara is frequently

described. Gay's case had mixed deafness which has been reported by others such as Nager (1948) of Zurich.

XX. SKIN AND ACCESSORIES

(*See also* ¶'*s 94, 108, 120, 125, 182, 281, 292.*)

267. Kloepfer, Krafchuk, Derbes, and Burks described and pictured *hereditary multiple leiomyomas* of the skin in 2 siblings and their half first cousin.

268. Wheeler, Shaw, and Cawley found *branchial cysts and sinuses* in 4 members of three generations of one family. The trait was considered autosomal dominant. Cysts, sinuses, and skin tabs containing cartilage occur in a line extending from a point anterior to the external ear to the anterior border of the sternomastoid muscle at the level of the angle of the mandible and thence along the anterior border of this muscle to a point near its attachment to the sternum.

269. The nomenclature, differential diagnosis, and histologic features of *cutis laxa* were discussed by Robinson and Ellis. It is a rare entity apparently distinct from the Ehlers-Danlos syndrome. Some features resemble the pendulous fibroma molluscum of neurofibromatosis.

270. The Lambert family of England containing many cases of *ichthyosis hystrix gravior* has found its way into genetic textbooks as an example of Y-chromosome inheritance. Some ingenious and dogged sleuthing by Penrose and Stern led to the conclusion that the trait was in fact probably an autosomal dominant in this family.

Hanssler reports a family in which 3 of 4 children were born with severe ichthyosis congenita. Two of the affected children died at 12 days and 6 weeks. The last-born affected child was treated with cortisone with dramatic results. Started at the third day of life the cortisone had had remarkable effects by the fourth day of treatment. The cortisone was stopped at 6 months when the child developed severe otitis media. Photographs showed perfectly clear skin several months after cessation of cortisone. At 18 months the child seemed perfectly well in all respects. The parents were not related.

271. Lamy, Garcin, Duperrat, and others reported a case of *incontinentia pigmenti* (Bloch-Sulzberger's disease) in a female infant. The family history was negative. A papular eruption was replaced by pigmentary spots of chocolate-brown color and of spattered shape, arranged in stripes, particularly on the side of the thorax. (Other observations suggest irregularities in the genetics justifying close examination.)

272. Church found a family history in 34 per cent of 918 patients with *psoriasis.* Ingram, also dealing with a Yorkshire population, had recorded a figure of 33.9 per cent. (This form of reporting is to be discouraged since as

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Steinberg points out, with apologies to Gilbert and Sullivan, one does not know how many of "his sisters and his cousins and his aunts" were known to the proband-informant.) Interestingly, the earlier the onset of the disease the greater the likelihood of a positive family history.

Hargreaves and Hellier could find no ABO blood group associations with psoriasis.

XXI. TEETH

273. By the twin method Osborne and collaborators demonstrated a strong genetic component in the variability in dimensions of the anterior permanent teeth. It was of interest that in regard to dental caries the teeth showing the most marked difference in concordance rates between monozygotic and dizygotic twins were those most exposed to the saliva (Horowitz, Osborne, and de George). The suggestion was made that genetic differences in the saliva may be the basis for the observations.

XXII. URINARY SYSTEM

274. Burkland gave a useful review of the literature on genetic abnormalities of the urinary system and genital system. Mudge reviewed the various genetic defects of renal tubular function: renal glycosuria, nephrogenic diabetes insipidus, renal hypophosphatemia, simple xanthinuria, essential cystinuria, simple glycinuria, the Fanconi syndrome, and atypical multiple defects.

275. Proved or probable cases of *Wilms' tumor* occurred in three generations of one family (Strøm).

276. Unilateral multicystic kidney disease is apparently an entity distinct from bilateral polycystic kidney disease (Conca and De Nicolai). It is less clearly genetic in causation than is the bilateral disease.

In 3 cases reported by Brihaye and Toppet the association of polycystic kidneys and cerebral aneurysms was again illustrated.

277. Nathan made observations on aberrant inferior polar renal arteries curving around and compressing the normal renal vein. The frequency was 7 in 200 autopsies. Six were on the left, one on the right. If the artery compresses the vein when the subject is upright, orthostatic albuminuria might result. Furthermore, compression of the artery by the vein might contribute to hypertension. Information on the genetics of aberrant renal artery is meager.

278. The *de Toni-Fanconi syndrome* (Harrison; Kuhlencordt; Reubi; Lowe) is characterized by resistant rickets, glycosuria, hyperaminoaciduria, and organic aciduria including "phosphate diabetes." Fundamentally there is a defect in renal tubular reabsorption of phosphorus, amino acids, and glucose and an impaired ability to resorb base without acid. The causes are multiple: Heavy metal poisoning, e.g., lead poisoning, can cause it. Accumulations of

copper in Wilson's disease cause it. Inhibition of sulfhydryl-dependent enzymes appears to be involved. Impairment of urate reabsorption with low serum uric acid occurs in some cases. Worthen and Good reported upon 2 patients, from the same family, with cystinosis proved by the demonstration of typical cystine crystals in the cornea and bone marrow. Cystinosis, a previously well-recognized basis for this syndrome, is inherited as an autosomal recessive.

279. Aschner and Gartler found that the diuresis curves after the rapid ingestion of 1,000 c.c. of water are much more similar in MZ twins then in DZ.

280. Gjone saw *renal glycosuria* in 7 individuals in three generations of one family.

281. Angiokeratoma corporis diffusum of Fabry is a familial disorder which until the report of Colley and others had apparently been described only in men. Renal needle biopsy in 2 male first cousins with the characteristic skin lesions (small elevated purplish lesions in the "bathing trunks area") revealed characteristic changes: vacuolization and distention of the cells of the glomerular tufts and distal tubules. Urine-concentrating ability was markedly impaired in both and in one the glomerular filtration rate was moderately reduced. Retrospective review of the autopsy of the mother of one of the men revealed the same histologic changes. The woman had died in uremia at the age of 47 years. Since she was said to have had no skin lesions, the authors speculate that women may have internal manifestations of the genetic defect even though skin lesions are lacking. If true, the exclusively male involvement reported in the literature might have explanation. It is to be noted that the men were cousins through their mothers. Is the trait sex linked?

282. Perkoff and associates in Utah, and Sturtz and Burke at the Mayo Clinic reported follow-up studies on families with chronic *familial nephritis* they had previously described. In the Utah family constant pyuria and intermittent episodes of fever and bacteriuria suggested pyelonephritis. In the Mayo Clinic family the clinical pattern was more that of chronic glomerulonephritis. It is not certain, however, that a different disease is involved. For this reason Perkoff suggested the designation of chronic hereditary nephritis. Males were usually more severely affected than females. Histologically, there were signs suggesting both interstitial pyelonephritis and glomerulonephritis (Perkoff). In addition, there was at least one possibly unique feature, foam cells near the tubules. Most affected individuals had progressive nerve deafness. No ocular manifestations, such as spherophakia and cataract described by Sohar and others, were found. Most reported pedigrees are too fragmentary to provide more than corroborative evidence on the mode of inheritance. The large Mormon pedigree from Utah suggested partial (incomplete) sex linkage on first analysis in 1951. The findings of the follow-up are still consistent with the hypothesis.

For application of the Haldane test for partial sex linkage, the data can be arranged as shown in this table:

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OFFSPRING OF AFFECTED MALES

	AFFECTED	UNAFFECTED
Sex same as affected grandparent	24	*5*
Sex different from affected grandparent	*2*	18

In this particular family all affected grandparents were female. Exceptions to the expected are represented by the italicized figures. Since some females have the disease in mild form, reduced penetrance may account for the 5 females who were classified as unaffected or they may be the products of crossing-over between the homologous portion of the X and Y chromosomes. The 2 males who were affected may, in fact, have had a different renal disease, or they too may be the result of crossing-over.

Morin and colleagues also reported on "familial hematuric nephropathy."

283. Under the title *familial juvenile nephronophthisis* Hackzell and Lundmark described two families each with 2 sibs suffering from a renal disease probably of the type reported by Fanconi and others in 1951. The renal disease had its onset with polyuria, polydipsia, and nocturia at the age of 2 to 6 years. The specific gravity of the urine became fixed and progressive azotemia occurred. Remarkable features, however, were the almost complete absence of albuminuria, formed elements in the urinary sediment, and hypertension. In 3 autopsy cases, the renal changes were practically identical: symmetrical, diffuse renal contraction; severe glomerular and tubular damage; striking sheathlike, thickened parietal glomerular basement membranes, totally hyalinized glomeruli; areas of atrophic and hypertrophic tubules, some with a thyroidlike appearance.

XXIII. MISCELLANEOUS

284. Stormont reviewed "genetics and disease" in animals. The following sections also are related to *comparative genetic pathology:* ¶'*s* 8, 24, 51, 63, 65, 66, 108, 171, 200, 202, 212, 224.

285. Scarabicchi reported on multiple cases of *poliomyelitis* in families. While consistent with the genetic hypothesis advanced by Nash Herndon on the basis of a study of twins (1952), the findings in the study do not provide specific support for the hypothesis.

286. McKusick and Fisher described two families in each of which at least 2 sibs seem to have had what might be termed *hereditary miliary bronchoalveolar cystic disease* or more simply congenital cystic disease of the lung. The points emphasized, in addition to the probable genetic basis of the defect, were as follows: (1) clubbing of the fingers may antedate symptoms or x-ray evidence of the lung disease by decades, (2) the clinical picture may be that of progressive idiopathic pulmonary fibrosis with the alveolocapillary block syndrome and/or cor pulmonale, (3) bronchogenic carcinoma may be a fatal complication.

287. R. A. Fisher collected data on the *smoking habits* in a group of twins catalogued in von Verschuer's Institute at Münster. Only 24 per cent of the monozygotic twins were different with regard to smoking habit or preference for cigarettes, pipes, or cigars, whereas 51 per cent of dizygotic twins differed. Fisher suggests a genetic basis for the smoking habit and the form it takes. Furthermore, he thinks the association of smoking and lung cancer is merely due to the fact that the same genotype predisposes to both. However, although no critical study has been reported, lung cancer in man does not seem to have a particular genetic background.

288. Schull and Neel reconsidered the question of *sex-ratio* in the children of persons exposed at Hiroshima and Nagasaki and reversed their previous conclusion. It is now their impression that the data are consistent with the production of sex-linked recessive mutations by *radiation.*

Shettles suggested that the high primary sex ratio (more males are conceived than females in all human populations) may be due to the lighter weight of the male determining sperm which contain a Y-chromosome rather than an X-chromosome. On the other hand, in utero and in every age group more males than females succumb. In 42 species including invertebrates, vertebrates, and mammals, the female outlives the male. The over-all higher mortality in the male cannot be attributed to abuse of alcohol and tobacco, physical and emotional stress, etc., although these may be aggravating factors. Shettles speculates that the difference may reside in the larger genetic endowment of the female with her two X-chromosomes.

Bernstein proposed that the rise in the sex ratio observed near the end of or just after a major war may have its explanation in a higher proportion of males being born after short sexual exposures. He found that first offspring born in the first 18 months of marriage were 55.3 per cent male, whereas when the first child was not born until some time later than the first 18 months after marriage, only 49.8 per cent were male. The "more rapidly fertile" group, as he termed the first one, was more likely to have sons as first born.

On the basis of U.S. birth data for the year 1955, Novitski and Kimball analyzed further the variation in the proportion of male birth (i.e., the secondary sex ratio as opposed to the primary sex ratio at fertilization) as a function of birth order and parental age. Novitski (1953) had noted little or no effect of maternal age whereas increasing age of the father correlated with a decreasing sex ratio. This was a puzzling result since whereas one could readily imagine a maternal effect through differential fetal mortality a paternal effect would be less easily explained. The new study again demonstrated independence of sex ratio and maternal age and a dependence on both birth order and paternal age. Furthermore, a highly significant interaction between birth order and age of father was demonstrated. The authors suspect that birth order and paternal age show this effect because they are themselves correlated with other factor(s) more closely related to the true causes of variations in sex ratio.

In 1889 Geissler published data on the sex ratio in sibships collected in Saxony for the period 1876-1885. Some four million births were recorded through

a requirement that the parents state the sex of all their children on birth certificates. The resulting data have been subjected to re-analysis on several occasions. The latest analysis, by Edwards, arrives at the conclusion that there is no evidence for the existence of parents capable of producing unisexual families. The data can be accounted for, Edwards feels, by variability within families of p, the probability of a birth being male. The variance of p was estimated to be about 0.0025.

289. Jones and Doig observed Boeck's *sarcoidosis* in twins thought to be monozygotic. They reviewed the suggestive, if not impressive, array of reports of this disease in twins and multiple members of the same family. Warin saw sarcoidosis in multiple family members. (The racial differences in the incidence of sarcoidosis and these twin and family studies suggest that this disease of unknown etiology may represent a genetically determined pattern of reaction to multiple and diverse agents—a hypothesis advanced by Hoyle [1954], according to the authors.—Ed.)

290. In an article entitled "Normal Young Men" Roger J. Williams amplified on the theme stated succinctly in the title of his monograph, *Biochemical Individuality.* He suggests that correlation of patterns of biochemical individuality with disease susceptibility should be profitable—a modified "constitution and disease" approach. One of the best parts of the article is a quotation he ascribes to Parry, the English physician of the eighteenth century: "It is more important to know what sort of patient has a disease than to know what sort of disease a patient has."

291. F. Clarke Fraser gave a "level-headed" summary of *genetic counseling* in some common pediatric diseases: anencephaly and spina bifida aperta, cleft lip and/or palate, clubfoot, congenital heart disease, diabetes, epilepsy, Mongolism, and others.

292. Heller and colleagues of Tel Aviv provided a detailed description of a condition they called *familial Mediterranean fever.* The condition occurs mainly in Armenians and in Sephardic Jews (Jews who left Spain during the Inquisition and settled in various countries bordering the Mediterranean). The authors had 74 patients: 50 males and 24 females. In 60 per cent more than one member of the family was affected. In one family three generations and in three families two generations were affected. Consanguinity was apparently not a factor. The disease is characterized by short recurrent bouts of fever accompanied by pain in the abdomen, chest, or joints and an erysipelas-like erythema. Most of the patients are subjected to at least one laparotomy. The sedimentation rate is increased but the white count is usually normal. Cortisone is ineffective. Amyloidosis may develop late.

293. Farquhar and colleagues at the Royal Edinburgh Hospital for Sick Children described so-termed *familial haemophagocytic reticulosis* in all four mem-

bers of a sibship. Two girls and a boy died of the disease. In the fourth child the disorder was milder. Severe anemia and leukopenia, the cardinal features, seem to be due to excessive phagocytosis of blood cells. An autoantibody and shortened red cell life span were noted in the father. Although the disease is not proved to be hereditary, the possibility must be kept in mind.

EPILOGUE

The choice of the term *medical genetics* deserves comment. In recent years the development of programs of genetics in medical schools has prompted discussions of the best designation. *Medical genetics* is criticized by some because they fear that the impression is conveyed that the discipline is concerned only with sick people, that it has a therapeutic armamentarium at its disposal, and that it spurns any aspects which do not have immediate and obvious implications to disease in man. *Clinical genetics* is, in fact, the term which best designates the branch of medical genetics these critics have in mind. *Human genetics* is criticized as being too restricted for the material which should be investigated and taught in medical schools. For example, bacterial genetics can be construed as medical genetics but not as human genetics.

We have used *medical genetics* in the title of these reviews and of our Division. We suggest the following definition of medical genetics: *any genetic investigation or teaching which is done or might legitimately be done in a medical school.* It may be that, in due course as separate departments are created in medical schools, each will be referred to simply as the Department of Genetics in the School of Medicine of Such-and-such University. Problems of semantics will thereby be diminished, but it is hoped that the broad concept of genetics in medicine will not be sacrificed merely for the sake of a semantic armistice.

The unity of medical genetics "across the board" is an impressive feature and a feature which represents its main strength. Medical genetics is essentially the biology of man, including the biology of other forms of life interacting with man, and of forms of life that shed light on biologic mechanisms in man. The challenge represented by the broad scope of medical genetics is a source of fascination which, it is hoped, will attract good minds to this branch of medicine.

In many quarters a state of mutual admiration exists between persons doing "basic"* research and those dealing with patients. Increasingly, clinical departments are sponsoring research as "basic" as any done in other departments of the University. Young M.D.'s are acquiring competence in techniques which permit them to do in man investigations which are as precise and as fundamental as any done in microorganisms.

Let us have it clear. The clinician and the scientist, in so far as they are separate individuals—and fortunately they are slowly becoming more often one—need each other in the field of medical genetics more perhaps than in any other field. Let there be no underrating by either of the contribution of the other. It is helpful to read Beadle's Nobel lecture (Science 129:1715, 1959) in which he points out that the one-gene-one-enzyme concept is properly credited to

*This badly overworked and ill-defined term is used for want of a better.

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Sir Archibald Garrod, physician and biochemist, who expounded the principle on the basis of alkaptonuria in the early years of this century:

> Despite the simplicity and elegance of Garrod's interpretation of alcaptonuria and other inborn errors of metabolism as gene defects which result in inactivity of specific enzymes and thus in blocked reactions, his work had relatively little influence on the thinking of the geneticist of his time. Bateson's *Mendel's Principle of Heredity* and a few other books of its time discuss the concept briefly. But up to the 1940's no widely used later textbook of genetics that I have examined even so much as refers to alcaptonuria. . . . At that time we were unaware of Garrod's work, partly because geneticists were not in the habit of referring to it and partly because we had failed to explore the literature. . . . In this long, roundabout way, first in *Drosophila* and then in *Neurospora* we had rediscovered what Garrod had seen so clearly so many years before. By now we knew of his work and were aware that we had added little if anything new in principle.

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Illustrations of the other side of the coin—delay, in application to man, of fundamental genetic principles worked out in lower forms—are too numerous to cite. Whereas biochemical genetics had its inception in man the following branches of genetics started in other forms and have been, sooner or later, incorporated into medical genetics: (a) Mendelian genetics, (b) genetic linkage, (c) cytogenetics, and (d) population genetics.

In discussing the place of genetics in the medical curriculum, three phases of the problem can be discussed: (1) the organization, departmentally, of instruction; (2) the specific curriculum; and (3) what the ideal medical geneticist should be, that is, what our goal sho ld be in graduate training.

There are three main patterns taken by medical schools in this country in *the organization* of medical genetics programs:

1. Separate departments of genetics (or human genetics, or medical genetics) exist at Michigan, Wisconsin, and Stanford. Separate departments of anatomy, biochemistry, and physiology are entirely justified, all are agreed, even though top-notch physiology and biochemistry are done in clinical departments and electron microscopes are not confined to departments of anatomy. Similarly a separate department of genetics can be justified even though it is realized that genetics will not be studied only by that department.

2. A second pattern involves the creation of a Division of Genetics within an existing department. Anatomy or biochemistry on the preclinical side and preventive medicine, pediatrics, or internal medicine on the clinical side are departments in which such divisions may exist. Usually many features of the third pattern coexist with this divisional pattern. The University of Washington and The Johns Hopkins University each have a Division of Medical Genetics in the Department of Medicine.

3. Depending on the personalities, geography, departmental barriers, and other aspects of the local situation, it may be possible for a strong and effective interdepartmental program in human genetics to develop. One or more persons in each of the following departments may profitably participate: anatomy, biochemistry, microbiology, pathology, preventive medicine, biostatistics, and any or all of the clinical departments, especially medicine and pediatrics.

The Curriculum.—At the undergraduate level, the best program seems to be an introduction to general genetics in the first year, possibly as part of the anatomy course, and repeated exposure thereafter as part of instruction in biochemistry, microbiology, pathology, and preventive medicine and of all the clinical instruction. General genetics should be assigned a specific allocation of time; further attention can be given as an integral part of other instruction, whether in the form of lectures, seminars, or clinics.

In addition the interested and competent student can be permitted to elect work in the graduate curriculum. A graduate curriculum we have found satisfactory is the following: *First quarter.* Intensive and extensive survey of general genetics. Lectures. *Second quarter.* Methods in human genetics. Practical aspects of pedigree collection and analysis, statistical testing of genetic hypotheses, marker traits, linkage analysis, cytogenetics. Lectures and laboratory. In the laboratory, problems based on data from the literature or from current work are presented and the practical methods are demonstrated and practiced. *Third and fourth quarters.* A survey of medical (i.e., clinical) genetics. What is reliably known of the operation of genetic factors in all areas of medicine is reviewed. Guests from various clinical departments participate. Illustrative material is used abundantly and patients are demonstrated when available and appropriate to the topic of discussion.

In addition, at Hopkins a series of lectures, given usually (it is planned) by a guest lecturer and open to the entire University staff and student body, is offered each year. The themes planned for these lectures are as follows:

1. A survey of human genetics. 12 lectures.
2. A survey of biochemical genetics. 8 lectures.
3. A survey of clinical genetics. 12 lectures (by various lecturers).
   Etc.

In the graduate curriculum listed above students will participate for no less than one year, of course. Two-year participation will be urged. Each student conducts a research arbeit parallel with the more formal instruction. Most of the students are physicians who have already had clinical and research training in some subspecialty area and who wish to add genetics to their armamentarium for research, teaching, and patient care. Thus far in our own curriculum, graduate students have had a background in cardiology, hematology, gastroenterology, preventive medicine, pediatrics, and pathology, as well as general internal medicine. One is a nurse training for field work, pedigree tracing, and family studies in medical genetics.

What should *the ideal medical geneticist* be like? If I could draw and were to try to represent him for you, the ideal medical geneticist would look something like one of the gods with many arms represented in the idols of Indonesian art. In one hand he would be balancing an entire set of the *Oxford System of Medicine*; in a second hand he would hold several textbooks of general genetics including a book or two on cytogenetics; in a third hand, several textbooks and monographs on embryology; in a fourth, several biochemistry textbooks, including some on enzyme chemistry; in a fifth, several biostatistics texts and a few on epidemiology;

in a sixth, texts on immunochemistry and blood group serology. The figure would probably be seated on a firm foundation of knowledge and understanding of the history and culture of the human species. But it might be upright, like the dancing Indonesian idols, for safaris to investigate peoples in many parts of the world have become a prominent feature of studies in human genetics. If so, it will be necessary for the figure to balance textbooks of physical and social anthropology on the top of his head!

Few individuals will have the capacity and patience to attain this idealized goal. However, unless we set some objective such as this, the purposes of our graduate curricula may be unclear.

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